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Clinical Evaluation of a Novel Liquid Formulation of L-Thyroxine for Once Daily Treatment of Dogs with Hypothyroidism

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Background: A liquid solution of levothyroxine (L-T4) is available for treatment of canine hypothyroidism.

Hypothesis: Once daily oral administration of a liquid L-T4 solution is effective and safe for controlling hypothyroidism in dogs.

Animals: Thirty-five dogs with naturally occurring hypothyroidism.

Methods: Dogs received L-T4 solution PO once daily at a starting dosage of 20 μg/kg body weight (BW). The dose was adjusted every 4 weeks, based on clinical signs and peak serum total T4 (tT4) concentrations. Target peak serum tT4 and thyroid stimulating hormone (TSH) concentrations, 4–6 hours posttreatment, were 35–95 nmol/L and < 0.68 ng/mL, respectively. Dogs were followed for up to 22 weeks after establishment of the maintenance dose.

Results: Clinical signs of hypothyroidism improved or resolved in 91% of dogs after 4 weeks of L-T4 treatment at 20 μg/kg once daily. The maintenance dose was established in 76, 94, and 100% of dogs after 4, 8, and 12 weeks of treatment, respectively. This was 20 μg L-T4/kg BW for 79% of the dogs, 30 μg/kg BW for 15%, and 10–15 μg/kg BW in the remaining 6%, once daily. Thereafter, median peak tT4 and TSH concentrations were 51 nmol/L and 0.18 ng/mL, respectively, and remained stable during the 22-week follow-up; clinical signs did not recur.

Conclusions and Clinical Importance: All of the hypothyroid dogs had rapid clinical and hormonal responses to supplementation with the PO-administered L-T4 solution. The starting dosage of 20 μg L-T4/kg BW once daily was suitable for 79% of dogs.

Key words: Canine; Clinical trials; Replacement therapy; TSH.

Hypothyroidism is one of the most common endocrine diseases in dogs.[1] Approximately 95% of cases are primary (thyroidal) in origin and caused by lymphocytic thyroiditis or idiopathic atrophy of the thyroid gland.[1] With either process, there is progressive destruction of the thyroid gland over time. Clinical signs of hypothyroidism become apparent when more than 75% of the gland has been destroyed.

Diagnosis of hypothyroidism can be challenging because most of the clinical signs are not specific. Hypothyroid dogs usually have low total T4 (tT4) and high thyroid stimulating hormone (TSH) concentrations. However, a number of nonthyroidal illnesses[2] and drugs[3] can substantially decrease thyroid hormone concentrations, often to concentrations below the reference range, leading to a false-positive diagnosis of hypothyroidism. Free T4 concentration (fT4) is reported to be less affected by nonthyroidal factors than tT4. A high specificity (98%) for diagnosing hypothyroidism in dogs was reported when fT4 was used in conjunction with TSH.[4] However, results still may be conflicting and, according to Dixon and Mooney,[5] thyroglobulin autoantibody (TgAA) results initially may be needed to support the diagnosis of hypothyroidism.

In affected dogs, daily levothyroxine (L-T4) replacement therapy is required for life. Treatment corrects abnormal tT4 and TSH concentrations within 2 weeks of initiating therapy.[6] Clinical signs such as lethargy reportedly improve within the 1st week of therapy, whereas alopecia, hyperpigmentation and other skin manifestations may take several months to resolve.[6] The objective of L-T4 supplementation is to determine a dose that controls clinical signs without inducing toxicosis. Several different doses and regimens have been recommended for L-T4 oral supplementation in hypothyroid dogs, varying from 11 to 44 μg/kg body weight (BW) either once or twice daily. Poor owner compliance is a common cause of treatment failure, thus efforts to simplify the dosing schedule from twice-a-day to once-a-day supplementation may help with regulation. Recently, the pharmacokinetic properties of a liquid formulation of L-T4 sodium[a] were evaluated in healthy dogs.[7] The results of that study supported the hypothesis that once daily administration may be sufficient to achieve adequate control of hypothyroidism in dogs.

In the present study, the efficacy and safety of once daily treatment with a PO-administered L-T4 sodium solution[a] was evaluated in hypothyroid dogs under clinical conditions.

Materials and Methods

Clinical Cases

The study was designed as an open, noncontrolled, multicenter field trial. Between November 2004 and June 2006, 92 dogs of various breeds with suspected primary hypothyroidism were presented for inclusion in

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Belgium, France, Germany, Ireland, and the United Kingdom. Dog owners were informed about the relevant details of the clinical study and confirmed agreement to participate in the trial by signing an informed consent form. All of the information from the present study was collected from clinical cases using standardized case record forms.

Diagnosis of Hypothyroidism

Dogs were presented with clinical signs suggestive of hypothyroidism. Standardized physical examination of each dog with special focus on the most frequent clinical signs of hypothyroidism (eg, overweight, obesity, apathy, exercise intolerance, alopecia, hyperpigmentation) was performed at inclusion. A score was attributed to each sign: body condition as normal, thin, overweight, or obese; activity as normal, apathetic, or hyperactive; exercise intolerance as absent or present; and alopecia, hyperpigmentation, and other signs as absent, mild, moderate, or severe. Subsequently, each clinical sign reported at inclusion was awarded a score at each visit to evaluate time to improvement or disappearance. The history of each case was examined to exclude euthyroid sick syndrome and confounding effects of previous drug therapy known or suspected to affect thyroid function (eg, antithyroid drugs, glucocorticoids, nonsteroidal anti-inflammatory drugs, trimethoprim-potentiated sulfonamides, antiepileptics, anesthetics, sedatives, furosemide, mitotane, penicillins, androgens, or dopamine within 6 weeks of inclusion). Dogs that had received thyroid hormone replacement therapy within the previous 8 weeks also were excluded. Patients with concomitant endocrine disorders (eg, insulin-dependent diabetes mellitus, hyperadrenocorticism, hypoadrenocorticism) and with chronic renal or hepatic failure also were excluded. Routine laboratory examination (CBC and serum biochemistry) was performed in all dogs at inclusion.

Hypothyroidism was confirmed and the dog included in the study if fT4 $\leq$5.4 pmol/L and TSH $\geq$0.68 ng/mL. If TSH was $<$0.68 ng /mL and fT4 $\leq$5.4 pmol/L, a positive TgAA test result was required for inclusion.[5]

Treatment Procedure and Follow-Up

Treatment was initiated with PO-administered L-T4 solution[a] at a starting dosage of 20 μg/kg BW once daily. Owners were asked to standardize the diet and timing of treatment related to feeding. During the initial treatment period (adjustment phase), dogs were reexamined every 4 weeks to evaluate clinical and hormonal response to treatment and to modify the L-T4 dose using 10 μg/kg increments, if needed. At each visit, peak serum tT4 and TSH concentrations were evaluated 4–6 hours after treatment. The target therapeutic range for tT4 was 35–95 nmol/L.

Once clinical signs of hypothyroidism had improved or disappeared and tT4 concentration was within the target therapeutic range, the L-T4 dosage was considered established, the adjustment phase ended, and the maintenance phase started. During this phase, the long-term efficacy of oral L-T4 supplementation of hypothyroid dogs was investigated by evaluation of both clinical and hormonal responses at 9 and 22 weeks after establishment of the correct dose (follow-up and final visits, respectively). At each visit, peak tT4 and TSH concentrations were evaluated. At the final visit, routine clinical pathology examinations were performed for all of the dogs in the study.

Adverse events observed during the study were recorded to assess the safety of long-term treatment with PO-administered L-T4 solution in dogs with hypothyroidism.

Sample Collection and Thyroid Hormone Measurements

At inclusion, a 5-mL blood sample was collected in a dry tube and serum prepared, kept refrigerated and sent, within 48 hours, to a centralized laboratory[b] for evaluation of serum fT4, tT4, and TSH concentrations.

At each subsequent visit during the adjustment and maintenance phases, a 2.5-mL blood sample was collected between 4 and 6 hours after treatment and serum prepared and sent to the centralized laboratory for evaluation of serum tT4 and TSH concentrations.

Electrochemiluminescence immunoassays were used to determine serum tT4[c] and TSH[d] concentrations. The method for determination of tT4 concentration in canine serum was validated by the centralized laboratory. The intra-assay coefficient of variation (over 10 consecutive assays) was 3.3% and the interassay coefficient of variation (assays over the course of 10 days) was 3.0%. The analytical sensitivity (limit of detection) was 5 nmol/L. The kit for the determination of TSH concentration was validated by the manufacturer for use in canine serum: intra-assay and interassay coefficients of variation (5 TSH concentrations, each concentration tested in duplicate twice daily over the course of 20 days) were 4.7–6.3% and 5.5–10%, respectively. The analytical sensitivity was 0.01 ng/mL. The method used for determination of serum fT4 concentrations[e] in canine serum, incorporating equilibrium dialysis combined with radioimmunoassay measuring fT4 concentration in the dialysate, had been validated by the centralized laboratory: the intra-assay coefficient of variation (over 10 consecutive assays) was 3.6% and the interassay coefficient of variation (assays over the course of 20 days) was 13.7%. The analytical sensitivity was 0.15 pmol/L. The limits of quantification were 0.03 ng/mL for TSH, 5 nmol/L for tT4, and 0.15 pmol/L for fT4. In dogs with TSH $<$0.68 ng/mL and fT4 $\leq$5.4 pmol/L, the presence of TgAA was tested using an enzyme-linked immunosorbent assay[f] validated previously for use in dogs.[8]

Data Handling and Statistical Analysis

Statistical analysis was performed using SAS 8.2 software.[g] The level of significance (α) was set at 0.05. Each dog was considered as its own control. Descriptive statistics (median, range) were calculated for each variable. Peak tT4 and TSH serum concentrations were considered as normalized or not, related to the target therapeutic ranges or values defined as 35–95 nmol/L and $<$0.68 ng/mL, respectively, based on results of a previously published study that used a similar dose rate and regimen.[6] In addition, tT4 and TSH concentrations and BW (calculated as a percentage of the dog's weight measured at inclusion) were analyzed, after log transformation, with analysis of variance for repeated measures, using a linear mixed model with time of treatment as fixed effects. When significant, values at each visit during treatment (establishment, follow-up, and final visits) were compared with values measured at inclusion visit using Tukey's multiple comparison test. Routine laboratory variables were considered as normal or abnormal, in comparison with the reference range defined by the centralized laboratory.

Results

Clinical Cases

Ninety-two dogs were screened. In 57 of these dogs, the diagnosis of hypothyroidism was not confirmed by the results of the hormone analysis, corresponding to a drop-out rate of 62%. The remaining 35 dogs were included in the study. In addition to mixed breed dogs (n = 8), 17 pure breeds were represented, Labrador (n = 5) and Border Collie, Doberman, and Boxer (n = 3 each) being the most frequent. Included dogs, 14 males (8 intact and 6 castrated) and 21 females (12 intact and 9 neutered), aged 7 years (median; range, 3–13 years) and weighing 33 kg (median; range, 5–67 kg). Median (range)

values for tT4, fT4, and TSH concentrations were 7 nmol/L (5–14 nmol/L), 2.1 pmol/L (0.15–5.7 pmol/L), and 1.40 ng/mL (0.30–6.78 ng/mL), respectively. A positive TgAA test was necessary for inclusion in 11% (4/35) of the dogs. All of these 4 dogs presented with low serum tT4 concentrations at inclusion (range, 5–13 nmol/L).

Clinical signs reported at inclusion in the hypothyroid dogs are summarized in Table 1. Metabolic signs of hypothyroidism were observed in 89% of the dogs: overweight or obesity, apathy, and exercise intolerance being predominant. Dermatologic signs of hypothyroidism such as alopecia, hyperpigmentation, alopecia of the tail, altered coat condition, seborrhea, presence of scaling, and myxedema were reported (at least one of these findings) in 97% of the dogs. Abnormalities in serum biochemistry (increased cholesterol concentration, 80%; increased triglyceride concentration, 83%) and CBC (low erythrocyte count, low hemoglobin concentration, and low hematocrit in, 69%) also were frequently present in the dogs.

Treatment Variables

Two dogs were withdrawn from the study for reasons unrelated to treatment or hypothyroidism (ie, recurrence of chronic colitis before inclusion in 1 dog, and sudden death of 1 dog detailed in the section describing adverse events), before the maintenance dose was established. One additional case was lost to follow-up after the 1st adjustment period, when its maintenance dose had been established. A maintenance dose could be established in 33 dogs within 12 weeks, the maximum of 12 weeks being necessary for 1 dog only (Fig 1). The L-T4 dosage was established at 20 μg/kg BW after the 1st adjustment period in 76% of the dogs. An increase of the daily dosage to 30 μg/kg BW was successful in achieving the target therapeutic ranges at the next 4-week adjustment phase in 5 of the 5 dogs that had a low serum tT4 concentration at the 1st adjustment visit. A decrease in dosage to 10 μg /kg BW, based on excessively high serum tT4 concentration (112, 113, and 145 nmol/L), was required in 9% of the dogs. This dosage was the final maintenance dose in 3% of dogs. In another dog, the dosage was changed back to the starting dosage of 20 μg/kg BW following a recurrence of clinical signs of hypothyroidism after 4 weeks of treatment at 10 μg/kg BW. In the remaining dog, a further adjustment to 15 μg/kg BW, the final maintenance dosage for this dog, was required.

In total, the starting dosage of 20 μg/kg BW was the maintenance dose for 79% of the dogs. The remaining cases required a maintenance dosage of 10 μg/kg BW (n = 1, 3%), 15 μg/kg BW (n = 1, 3%), and 30 μg/kg BW (n = 5, 15%).

During the maintenance phase, additional dosage adjustments were required in 16% of the dogs, related to serum tT4 concentrations outside of the therapeutic target range at the follow-up visit. At the end of the study, after correction for the actual BW of the dog at the end of the trial (see ''Effect of therapy on clinical condition''), median L-T4 daily dosage was 24 μg/kg BW once daily (range, 12–42 μg/kg BW once daily).

Table 1. Clinical signs reported in 35 included hypothyroid dogs at inclusion.

	Frequency	
Signs	N	%
Metabolic signs		
No signs	4	11
Overweight/obesity	27	77
Apathy	27	77
Exercise intolerance	22	63
Dermatologic signs		
No signs	1	3
Alopecia	26	74
Hyperpigmentation	18	51
Alopecia of the tail	10	29
Thin hair/poor, dry or dull coat	7	20
Seborrhea	7	20
Dandruff/dry scaly skin	6	17
Myxedema	5	14
Skin thickening/hyperkeratosis	3	9
Pyoderma	2	6
Erythema	2	6
Comedones	1	3
Thin skin	1	3
Epidermal collarettes	1	3
Dry nose	1	3
Abnormal hematology/serum biochemistry		
Increased cholesterol concentration	28	80
Increased triglyceride concentration	29	83
Low erythrocyte count	25	71
Low hemoglobin concentration	29	83
Low hematocrit	14	40

Effect of Therapy on Thyroid Hormone Concentrations

From the visit when the correct dose was established, serum tT4 concentrations measured 4–6 hours posttreatment increased significantly, compared with inclusion (Fig 2). A median concentration of 51 nmol/L (range, 21–94 nmol/L) was measured at dose establishment. Subsequently, peak serum tT4 concentrations remained stable until the end of the study (median [range]: 43 nmol/L [10–112 nmol/L] and 58 nmol/L [18–142 nmol /L] at the follow-up and final visit, respectively). Peak serum tT4 concentrations were within the target therapeutic range in 65% of the dogs at the follow-up visit and in 79% of the dogs at the end of the study. In the remaining dogs, transiently low serum tT4 concentrations were measured at follow-up (32% of the dogs; median [range]: 24 nmol/L [10–32 nmol/L]) or final visit (17% of the dogs; median [range]: 29 nmol/L [18–34 nmol/L]) while clinical signs of hypothyroidism remained absent. In 2 dogs during the maintenance phase, serum tT4 concentrations above the upper limit of the therapeutic target range were observed once (112 and 142 nmol/L, respectively) without concomitant clinical signs of thyrotoxicosis.

From inclusion, serum TSH concentrations decreased significantly in all of the dogs (Fig 3). TSH concentrations were <0.68 ng/mL in 88, 87, and 93% of the dogs at dose establishment, follow-up and the final visit, respectively. Serum TSH concentrations >0.68 ng/mL

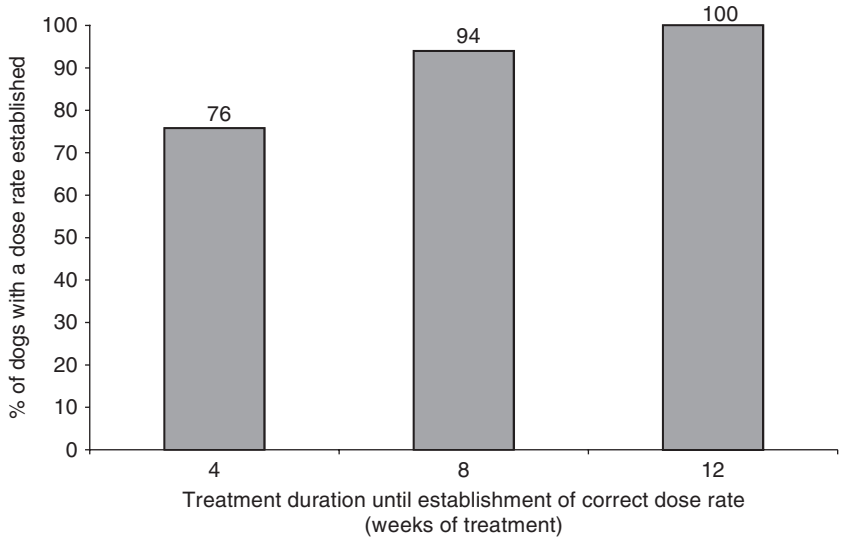

Fig 1. Cumulative percentage of dogs with clinical and hormonal hypothyroidism controlled with a PO-administered L-T4 solution plotted against time since onset of treatment.

were reported occasionally at both follow-up (n = 4) and the final visit (n = 2). In 2 of these cases, L-T4 dose was increased because of low concomitant serum tT4 concentrations. At the next visit, serum TSH concentrations regained target concentrations. In the remaining cases, the increased serum TSH concentration was transient and resolved without additional change in dosage. In 1 case, poor compliance with treatment was clearly identified as a cause of the transiently increased serum TSH concentration.

Effect of Therapy on Clinical Condition

Generally, metabolic signs improved within the 1st 4 weeks of treatment: apathy and exercise intolerance resolved in 88 and 90% of the dogs, respectively, within the 1st 4 weeks of treatment. In 2 dogs, time to disappearance of apathy, exercise intolerance or both was longer. In these dogs, serum thyroid hormone concentrations fell in the therapeutic target range only after 8 weeks of treatment, at a dosage of 30 μg/kg BW.

Body condition scored initially as overweight or obese had normalized by the final visit in 52% of the dogs. Body weight decreased during both the adjustment and maintenance phases, with a mean total decrease of 11.3 ± 10.0%, compared with inclusion (Table 2). In 23% of the dogs, BW loss was >20% (20.5–35.7%) by the final visit. The difference between BW reported at inclusion and at establishment visit (as % of inclusion value) was statistically significant ($P = .0085$) but stabilized thereafter.

Dermatologic signs resolved in 68% of the dogs by the final visit. Improvement or resolution of dermatologic signs of hypothyroidism was less rapid: alopecia, the most frequent dermatological sign reported, took a median duration of 109 days to resolve and still was not completely resolved in 4 dogs at the final visit (ie, after 175–212 days of treatment). Hyperpigmentation disappeared within approximately 3 months in 35%, within approximately 6 months in 24%, but had not yet resolved in 41% of the dogs after 172–301 days of treatment. At the final visit, alopecia of the tail was no longer reported; however, this condition took 3 months to resolve in 78% of the dogs and 6 months to resolve in

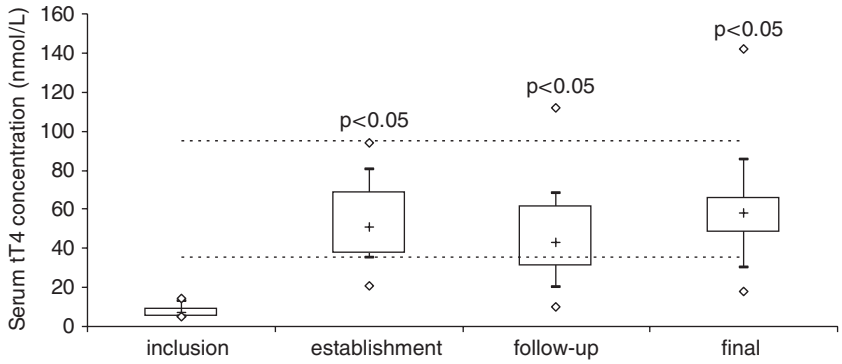

Fig 2. Box and whisker plots of serum tT4 concentrations in hypothyroid dogs at inclusion and from establishment of correct dosage to final visit, 4–6 hours after oral administration of L-T4. +, median; −, 1st and 9th decile; box, 1st and 3rd quartile; ◇, minimum and maximum; target therapeutic range [35–95 nmol/L] is indicated by a dashed line. Statistical significance of values versus inclusion levels is indicated.

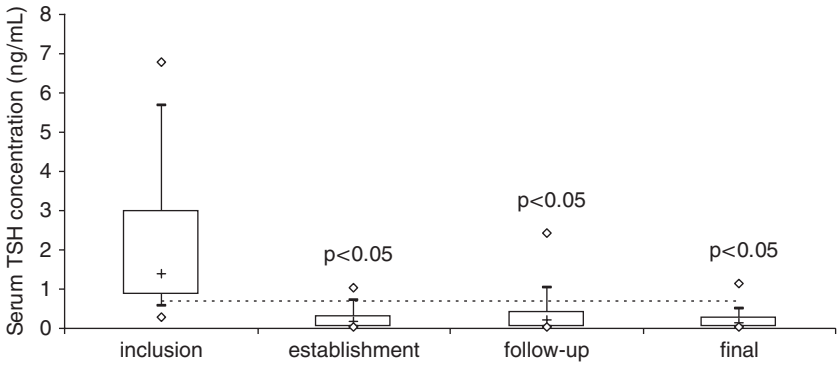

Fig 3. Box and whisker plots of serum thyroid stimulating hormone (TSH) concentrations in hypothyroid dogs at inclusion and from establishment of correct dosage to final visit, 4–6 hours after oral administration of L-T4. +, median; −, 1st and 9th decile; box, 1st and 3rd quartile; ◇, minimum and maximum; threshold value of 0.68 ng/mL is indicated by a dashed line. Statistical significance of values versus inclusion levels is indicated.

22% of the dogs. Altered coat condition resolved after 86–191 days of treatment with L-T4 in 71% of the dogs but still was present at the end of treatment in the 29% of the dogs (in one of these dogs, hair coat abnormalities had improved from severe to mild). Seborrhea resolved within 6 months of treatment with L-T4 in all of the affected dogs.

At the final visit, hypercholesterolemia had resolved in 75% of the dogs. In the remaining dogs, serum cholesterol concentrations either were close to the upper limit of the reference range (7.8 nmol/L) in 12.5% of the dogs (8.0, 8.4, and 9.0 mmol/L) or at least had decreased substantially (12.5% of the dogs). Serum triglyceride concentrations returned to within the reference range in 56% of the dogs but remained increased in 44% of the dogs, although in 4 of these dogs hypertriglyceridemia was moderate (<1.9 mmol/L) by the end of treatment. Anemia resolved completely in 79% of the dogs and partially in 16% of the dogs. In the latter, erythrocyte count and hemoglobin concentration improved but remained outside of the reference range. Anemia did not improve in 1 dog (5%) (values of 4.62×10^{12} cells/L for erythrocyte count and 11.1 g/dL for hemoglobin concentration at the final visit).

Adverse Events

Eight adverse events possibly were related to treatment. One 11-year-old poodle, with no history of cardiac disease, died suddenly after 47 days of treatment, coincident with occurrence of a heat wave. At the 1st adjustment visit for this dog, 11 days before death, no signs of congestive heart failure were reported, the heart rate was comparable to that at inclusion (126 versus 136 beats per minute, respectively) and peak serum tT4 concentration was lower than expected (18 nmol/L), promoting an increase in the dosage to 30 μg/kg BW. No further data on serum tT4 concentration or clinical condition were obtained before death and no postmortem examination was performed. Congestive heart failure was suspected by the veterinarian as the cause of death. Mild to moderate scaling that improved or resolved without discontinuing treatment was reported on 3 occasions, concomitantly with serum tT4 concentrations within the therapeutic target range. Altered coat color (reddish hair) was reported in 1 dog at the end of treatment. Vomiting after administration of the L-T4 solution was reported in 1 dog only when treatment was administered on an empty stomach. In a 2nd dog, vomiting occurred 3 times during the 1st 4 weeks of treatment and was not reported during the next 2 weeks before it was lost to follow-up. Finally, polyuria and polydipsia and concomitant high peak serum tT4 concentration (112 nmol/L) were reported at follow-up visit in 1 dog. After 4 weeks at 10 μg/kg BW, water consumption and serum tT4 concentration (30 nmol/L) had decreased, and serum TSH concentration (0.78 ng/mL) was high. No additional data were available due to death of the dog from pulmonary metastasis presumably from a mammary nodule detected at inclusion.

Table 2. Body weight of hypothyroid dogs at inclusion and from establishment of correct dosage until final visit.

		Body Weight (% inclusion)	
Visit	n	Median	Range
Inclusion	35	100	100–100
Correct dose establishment	33	94.7[a]	85.5–106.9
Follow-up	31	91.0[a]	77.1–104.3
Final	31	89.4[a]	64.3–107.1

[a]Significantly different from values at inclusion.

Discussion

The present study demonstrated that once daily treatment with a PO-administered L-T4 solution improved the clinical condition of hypothyroid dogs and returned serum tT4 and TSH concentrations to within the therapeutic target range. The response to treatment was rapid, within 4 weeks after initiation of treatment in most cases. As reported previously,[1] metabolic improvement in

response to L-T4 supplementation was observed rapidly after the onset of treatment whereas dermatologic signs took longer to resolve. Therefore, reassessment every 4 weeks during the adjustment phase was considered suitable for the evaluation of treatment. During the entire study period, peak serum tT4 concentration was selected for therapeutic monitoring of hypothyroidism. This choice was justifiable because this variable can be obtained routinely in veterinary practice and has been reported as sufficient, in conjunction with improvement of the clinical condition of the dog, for monitoring purposes in hypothyroid dogs.[6] The target therapeutic range for peak serum tT4 concentration also was selected based on this study[6] concluding that peak serum tT4 concentrations <35 nmol/L usually indicate a need to increase the L-T4 dose. The upper limit of 95 nmol/L was actually lower than that reported in the study (100 nmol/L) but was selected in order to avoid development of hyperthyroidism, signs of which were apparent in 2 dogs with serum tT4 concentrations >100 nmol/L in the study of Dixon et al.[6] At the final visit, median peak serum tT4 concentration was 58 nmol/L, similar to the concentration of 55 nmol/L reported by Dixon et al[6] in dogs with hypothyroidism treated with L-T4 tablets, based on their clinical response to therapy. Documenting a decline in serum TSH concentration during treatment has been used as an indicator of adequate treatment; increased values were associated with inadequate therapy in a previous study.[6]

In the present study, 79% of hypothyroid dogs were controlled with 20 μg L-T4/kg BW once daily, thus confirming the choice of this starting dosage. Because all of the dogs experienced marked clinical improvement after 4 weeks of treatment at this dosage, it appears that once daily supplementation using this PO-administered solution of L-T4 was not detrimental to well-being of the hypothyroid dogs, despite this dosage being half of the generally accepted recommendation of 20 μg/kg BW twice daily for L-T4 tablet formulations. The percentage of dogs with hypothyroidism controlled using ≤ 20 μg/kg BW once daily in the present study (85%) was higher than the 65% reported by Dixon et al[6] with L-T4 tablets. This finding may be related to a higher absorption of L-T4 from the liquid formulation compared with the tablet formulation after oral administration, in accordance with the 160% relative bioavailability calculated for L-T4 in a liquid versus tablet formulation in healthy dogs.[7] Furthermore, standardization of the timing of treatment in relation to feeding may have contributed to this phenomenon by decreasing the variability of absorption that is reported to be high for PO-administered L-T4 in dogs.[9]

Additional adjustments of the dosage were required occasionally during the course of the maintenance phase. Such adjustments are normal and emphasize the importance of lifelong therapeutic monitoring of serum tT4 concentration during L-T4 supplementation. The decision to adjust the dosage was based on serum tT4 concentrations only because clinical signs of hypothyroidism did not recur and there were no signs of thyrotoxicosis.

In contrast to metabolic and dermatologic signs, which resolved during the course of L-T4 supplementation, laboratory findings such as increased serum cholesterol and triglyceride concentrations and anemia persisted, although improved, in some of the dogs despite normalization of serum thyroid hormone concentrations. This finding has been reported previously[6] and suggests that laboratory results reflect overall response to L-T4 supplementation but cannot be used as criteria suitable for determination of adequate dosage.

No unexpected adverse effects were observed in this group of hypothyroid dogs after treatment with the L-T4 solution at dosages up to 40 μg/kg BW once daily for up to 6 months. A relationship between the development of scaling, reported in 3 dogs, and L-T4 supplementation cannot be ruled out and was considered probable because of the known links between thyroxine and skin and hair coat condition in dogs. An alteration in hair coat condition at initiation of L-T4 supplementation has been described previously in dogs.[6] However, the actual mechanisms involved in these events still are unknown. Concerning the sudden death of the poodle from cardiac failure during a heat wave, although unlikely, a relationship to treatment could not completely be ruled out, taking into account the recognized effects of thyroid hormones on cardiovascular function. For dogs with underlying cardiac disease, it may be advisable to introduce T4-therapy gradually, using a lower starting dosage than that used in the present study and increasing gradually until optimal control of both clinical and hormonal aspects of hypothyroidism is achieved.

During the study, special attention was paid to the timing of treatment in relation to feeding. Indeed, it has been demonstrated that administration of food concomitantly with treatment substantially decreases the bioavailability of L-T4 by approximately 45% in healthy dogs.[7] Therefore, the timing of treatment in relation to feeding was standardized for a single dog to keep L-T4 absorption on each day as constant as possible throughout the treatment period. In humans, certain food constituents, such as walnuts, liver, albumin, and soybean, have been shown to modify the bioavailability of PO-administered L-T4.[10,11] Although the diet of dogs generally is standardized, similar interactions between L-T4 and specific dietary constituents might exist. During the present study, it was recommended that the diet of the dogs be kept as constant as possible.

In the present study, special attention was paid to the diagnosis of hypothyroidism to ensure that included dogs were truly hypothyroid and not dogs suffering from euthyroid sick syndrome. The hormonal inclusion criteria were very stringent and not limited to measurement of serum tT4 concentrations only (a specificity of only 75% has been reported when diagnosis was based on evaluation of serum tT4 concentration only in dogs[12]). The detection and inclusion of only dogs with primary hypothyroidism, together with exclusion of dogs with euthyroid sick syndrome, is best achieved using concomitant measurement of fT4 and TSH concentrations, reported to have a sensitivity of 74% and a specificity of 98% in dogs.[4] The threshold concentrations applied

(5.4 pmol/L and 0.68 ng/mL, for fT4 and TSH, respectively) have been reported as optimal cut-off values in dogs.[12] The inclusion criteria selected in the present study were stringent enough to confirm the presence of primary hypothyroidism in all cases. Furthermore, the method for evaluation of fT4 concentration, after equilibrium dialysis, is the gold standard for this variable and provides reliable values.[13] Finally, the use of TgAA test in dogs with low serum TSH concentrations was in accordance with recent scientific findings.[5]

This multicenter clinical study demonstrates the efficacy and safety of a PO-administered L-T4 solution for treatment of spontaneous primary hypothyroidism in dogs. The starting dosage of 20 μg/kg BW once daily was sufficient to control both clinical and hormonal aspects of hypothyroidism in the majority of the dogs.

Footnotes

[a] Leventa 1 mg/mL, Intervet/Schering-Plough Animal Health, Boxmeer, the Netherlands
[b] IDEXX, Ludwigsburg, Germany
[c] Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany
[d] Immulite 2000 Canine TSH, Diagnostic Products Corporation, Los Angeles, CA
[e] FREE T4 by Equilibrium Dialysis, Nichols Institute Diagnostics, San Juan Capistrano, CA
[f] Test performed at Institute for Animal Physiology, University of Munich, Munich, Germany
[g] SAS Institute Inc, Cary, NC

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