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# Levothyroxine Tablet Efficacy Study in Dogs

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## Abstract

Fourteen (14) adult, client-owned dogs were diagnosed with hypothyroidism on the basis of TSH response testing, history, physical examination findings, hematologic and biochemical abnormalities. All dogs were administered levothyroxine (Thyro-Tabs<sup>®</sup> caplets) at an initial dosage of 0.022 mg/kg (0.01 mg/lb) PO q 24 hr. Resting energy expenditure (REE) of the dogs was estimated with an open flow indirect calorimetry system to determine the average rate of O<sub>2</sub> consumption (VO<sub>2</sub>) and CO<sub>2</sub> production (VCO<sub>2</sub>) per unit of time. The basal metabolic rate (BMR) values were calculated as Kcal/day/kg<sup>0.75</sup> and compared before and after therapy with levothyroxine (Thyro-Tabs<sup>®</sup>). The circulating T4 values, were also compared before and after therapy. The average post treatment BMR measurement (95.03 Kcal/kg/day) compared to the pretreatment measurement (80.61 Kcal/kg/day) was significant, p=.0451. The average posttreatment circulating T4 value (4.34 µg/dL) compared to the pretreatment T4 value (0.97µg/dL) was highly significant, p = .0002. The results of BMR and T4 measurements and improvement in clinical signs confirmed that Thyro-Tabs<sup>®</sup> caplets are effective in treating hypothyroidism in dogs.

## Study Site

The study was conducted at the Veterinary Teaching Hospital, Department of Clinical Sciences, Colorado State University, Fort Collins, Colorado, USA.

## Study Description

The purpose of the clinical field trial was to determine the efficacy of Thyro-Tabs<sup>®</sup>, levothyroxine sodium tablets, USP, in hypothyroid dogs and the effect of treatment on basal metabolic rate.

Fourteen (14) dogs were included in the study. The dogs ranged from three to ten years of age, with an average age of 6.2 years. Nine males, all but two had been castrated, and five spayed females were in the study. Ten different breeds were represented.

The dogs used in the study were presented or referred to the Veterinary Teaching Hospital with a low circulating basal T4 concentration and/or with clinical signs and clinical pathology results which supported hypothyroidism as a diagnostic possibility.

A dog was then confirmed as hypothyroid by a TSH (Thyroid Stimulating Hormone) stimulation and response test. A dog would be confirmed as being hypothyroid if its post-TSH T4 concentration was not double its pre-TSH T4 concentration and/or the post-TSH T4 concentration did not rise above the low normal range of 1.1 to 1.6 µg/dl. Additionally, another criteria was used to further delineate a diagnosis of hypothyroidism. If the post-TSH T4 concentration did not increase by an increment of 2 µg/dL, even though it may have demonstrated a two fold increase, a dog was classified as hypothyroid.

After confirmation of hypothyroidism, treatment was initiated with Thyro-Tabs caplets. Treatment was started at 0.022 mg/kg (0.01 mg/lb) of levothyroxine as a single daily oral dose with adjustments determined by circulating serum T4 concentrations or by clinical response to therapy. Variations to the recommended dosage and adjustment in dosage were made as necessary in each individual case.

Follow-up clinical evaluations and T4 measurements were to be conducted at monthly intervals for a four month period. Some variation in T4 measurement times occurred. The circulating serum T4 concentrations were measured by the radioimmunoassay (RIA) technique six to eight hours post-pill administration.

Basal metabolic rate (BMR) as measured by indirect calorimetry was determined for each dog before therapy was initiated and then again after a period of time of levothyroxine supplementation. BMR measurements were additional evaluation of response to therapy.

Indirect calorimetry is a method which estimates resting energy expenditure (REE) by measuring the amount of oxygen consumed ( $VO_2$ ) and carbon dioxide produced ( $VCO_2$ ) per unit of time. An open-circuit or ventilated flow-through system was used. Air is drawn through a mask at a rate ten times greater than the animal's predicted basal oxygen consumption rate using negative pressure created by a downstream vacuum pump. The percentage of  $O_2$  in a dried aliquot of the effluent gas is determined by an Ametek N-22  $O_2$  sensor (Ametek, Philadelphia) and Ametek S-3A/ $IO_2$  analyzer utilizing electrochemical cell technology.

Following a twelve hour overnight fast, a period of at least five minutes was allowed for the dog to adapt to the collection mask

and for the system to reach steady state. Data was collected for an additional 10 to 15 minutes and the average  $VO_2$  and  $VCO_2$  for this period was calculated. REE was calculated by applying the formula:  $REE(Kcal/day)=[3.9 \times VO_2(ml/min)]+[1.1 \times VCO_2(ml/min)] \times 1.44$ .

The BMR values used in this study were based on metabolic body size,  $Kcal/day/kg^{0.75}$

## Study Results and Discussion

The table on the next page provides a comparative summary between the fourteen clinical cases.

The mean pretreatment T4 measurements were compared by paired sample t-tests to the mean post-pill T4 measurements at the conclusion of the study. The mean difference (average increase of 3.36  $\mu g/dL$ ) of the T4 measurement at the end of the study (4.34  $\mu g/dL$ ) compared to the average pretreatment value (0.97  $\mu g/dL$ ) was highly significant,  $p = .0002$ . One dog did not show an increase in post treatment T4 values, even though it showed improvement in clinical signs. For most dogs an increase in circulating T4 values coupled with an assessment of clinical sign improvement provide the necessary evidence as to adequacy of the treatment regimen given to an animal.

In this study the effectiveness of Thyro-Tabs caplets in treatment of hypothyroidism was clearly evident by the average increase in T4 values.

The pretreatment BMR measurements were compared by paired sample t-tests to the average of the last BMR measurement made after a period of levothyroxine supplementation. The mean difference (average increase of 14.42  $Kcal/kg/day$ ) of the mean treatment BMR measurement (95.03  $Kcal/kg/day$ ) compared to the mean pretreatment BMR measurement (80.61  $Kcal/kg/day$ ) was significant,  $p = .0451$ . Four dogs showed no increase in

## Summary of 14 clinical cases receiving levothyroxine therapy

Case Number	Dog Name	Drug	*Dosage µg/kg/day	Initial T4 µg/dL	End T4 µg/dL	Initial BMR Kcal/kg/day <sup>0.75</sup>	Last BMR Kcal/kg/day <sup>0.75</sup>	Weight Decreased Increased Negligible
102772	Sonsie	Thyro-Tab	36.7	0.22	5.52	88.64	140.42	N
130701	Bud	Thyro-Tab	16.8	0.02	4.90	70.26	82.30	D
130433	Kala	Thyro-Tab	48.0	1.50	5.84	100.78	98.55	N
129366	B.G.	Thyro-Tab	50.0	0.62	1.79	131.93	87.55	N
131263	Buster	Thyro-Tab	37.5	0.02	8.57	84.31	88.69	D
129726	Taylor	Thyro-Tab	44.7	1.18	3.77	78.53	86.51	N
105061	Piglet	Thyro-Tab	21.6	1.60	2.18	103.49	126.51	N
131659	Rounder	Thyro-Tab	18.1	2.30	1.74	84.90	77.67	D
134728	Shredder	Thyro-Tab	39.5	0.16	4.25	58.29	98.62	D
133734	Spike	Thyro-Tab	19.0	0.16	4.42	80.46	106.30	D
120124	Bria	Thyro-Tab	19.4	2.20	3.25	73.23	69.98	N
137969	Chance	Thyro-Tab	14.2	0.64	2.85	72.05	87.71	N
134142	Zeke	Thyro-Tab	15.1	2.79	4.83	52.16	82.20	N
140539	Lefty	Thyro-Tab	19.3	0.22	6.79	49.52	87.41	D

\*Dosage at the conclusion of the study

## Summary of the descriptive statistics

	Dosage	Initial T4	End T4	Initial BMR	Last BMR
Number of Cases	14	14	14	14	14
Minimum	14.20	0.02	1.74	49.52	69.98
Maximum	50.00	2.79	8.57	131.93	140.42
Mean	28.56	0.97	4.34	80.61	94.32
Standard Deviation	13.33	0.95	1.96	21.79	19.06

the final BMR measurement compared to the pretreatment BMR measurement. One of these dogs had chronic renal failure. One dog (Kala) also had a low normal post-pill T4 concentration at the time the BMR was measured. Another dog (Rounder) also had borderline normal post-pill T4 value when the BMR measurement was made, but he showed good response clinically to the therapy. The fourth dog (Bria) with no increase in the BMR measurement after treatment did show good increase in post-pill T4 concentration and adequate clinical response.

The BMR measurements made before and after therapy further confirmed the efficacy of Thyro-Tabs caplets in increasing depressed basal metabolic rate in hypothyroid dogs. In general, the BMR increases after treatment reflected the T4 and clinical sign improvement.

### Clinical Response

The success of levothyroxine therapy, in addition to serum T4 concentrations and BMR measurements, also involved assessment of clinical response. Included in the evaluation of clinical response was improvement in skin and haircoat, increased activity, and weight loss.

Although complete resolution of presenting clinical signs had not occurred in most dogs at the conclusion of the study, every dog showed improvement, some dramatically. Several dogs were overweight and many were obese. Six dogs showed weight loss at the conclusion of the study. Some dogs had substantial weight losses. No dogs gained weight. Of the eight dogs that had negligible changes in their weights over the length of the study only two dogs (Taylor and Zeke) were overweight at the beginning of the study and remained overweight at the end.

Skin and haircoat complaints were part of the history for nine of the dogs in the study and all exhibited improvement in the skin and haircoat by the end of the study.

Increase in a dog's activity following levothyroxine supplementation was a common observation. The case records document increased or good activity in over 60% of the dogs in the study.

One dog was euthanized during the study because of reasons unrelated to levothyroxine therapy. It was euthanized because of chronic renal failure and secondary hyperparathyroidism.

The levothyroxine dosage used in the fourteen clinical cases ranged from a low of 14.2 µg/kg/day to a high of 50.0 µg/kg/day with an average dosage of 28.6 µg/kg/day. The average daily dose used in the study was higher than the 22.0 µg/kg/day that had been recommended for the study. Eight dogs were treated with doses less than the target dose of 22.0 µg/kg/day. Three dogs were treated with doses between 22.0 and 44.0 µg/kg/day. Three dogs were treated with doses greater than 44.0 µg/kg/day. The median dose used in the study was 20.5 µg/kg/day. The dosages used generally followed recommendations by recognized veterinary endocrinologists<sup>1,2</sup>. The dosage used has to be individualized for each case.

### Study Conclusions

Thyro-Tabs caplets is an effective dosage form of levothyroxine sodium in treating hypothyroidism in dogs. The initial recommended daily dose should be 22 to 44 µg/kg [0.1 mg to 0.2 mg per 10 pounds (4.5 kilograms)] in single or divided doses. The dosage may be adjusted depending on clinical response and post-pill T4 values.

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<sup>1</sup>Feldman, E.C., R.W. Nelson. 1987. Hypothyroidism. Pages 55-90 in *Canine and feline endocrinology and reproduction*. W. B. Saunders Company, Philadelphia.

<sup>2</sup>Nachreiner, R.F., K.R. Refsal, W.R. Ravis, J. Hauptman, E.J. Roser, W.M. Pedersoli. 1993. Pharmacokinetics of l-thyroxine after its oral administration in dogs. *AJVR* 54:2091-2098.