

# Use of recombinant human thyroid-stimulating hormone for thyrotropin stimulation test in euthyroid dogs

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**Abstract** — The purpose of this study was to evaluate the effects of the recombinant human thyroid-stimulating hormone (rhTSH) on serum total thyroxine (TT<sub>4</sub>) concentration in euthyroid dogs. Six healthy beagle dogs were used in each of the 3 phases of this study. Phase I: thyroid-stimulating hormone response tests were performed by using a total dose of 25 µg, 50 µg, and 100 µg of rhTSH, administered intravenously. Phases II and III: thyroid-stimulating hormone response tests were performed by using 50 µg of rhTSH administered by intramuscular and subcutaneous routes, respectively. In each phase and following all the administered doses of rhTSH, an increase in the serum TT<sub>4</sub> concentration was noted, although it was not always significant. For phase I, there was a significant increase in serum TT<sub>4</sub> concentrations. Based on this study, 50 µg was judged to be the optimal intravenous dose of rhTSH. For phases II and III, there was no significant increase in serum TT<sub>4</sub> after the administration of rhTSH. Results of this study suggest that rhTSH could be a good substitute for bovine TSH, when used by the intravenous route, for the TSH stimulation test in dogs. Further studies are required to confirm its clinical usefulness.

**R sum ** — Utilisation de la thyrotropine humaine recombinante lors de test de stimulation   la thyrotropine chez des chiens euthyroïdiens. Le but de cette  tude  tait d' valuer l'effet de la thyrotropine humaine recombinante (rhTSH) sur la concentration s rique de thyroxine totale chez des chiens euthyroïdiens. Six chiens Beagle en sant  ont  t  utilis s dans chacune des trois phases de l' tude. Phase I : des tests de stimulation   la TSH ont  t  effectu s en utilisant des doses totales de 25 µg, 50 µg et 100 µg de rhTSH administr e par voie intraveineuse (IV). Phases II et III : des tests de stimulation   la TSH ont  t  effectu s en utilisant 50 µg de rhTSH par voie intramusculaire (IM) et par voie sous-cutan e (SC). Une augmentation de la concentration s rique de la TT<sub>4</sub> a  t  not e (quoique pas toujours significative) suivant l'administration de chaque dose de rhTSH lors des trois phases. Au cours de la phase I, une augmentation significative de la concentration s rique de la TT<sub>4</sub> a  t  not e suivant l'administration de rhTSH par voie IV. Selon cette  tude, la dose de 50 µg de rhTSH a  t  jug e comme la dose optimale par voie IV. Au cours des phases II et III, aucune augmentation significative de la concentration s rique de la TT<sub>4</sub> a  t  not e suite   l'administration de la rhTSH. Les r sultats de notre  tude sugg rent que la rhTSH utilis e par voie IV pourrait  tre un bon substitut   la TSH bovine lors de tests de stimulation   la TSH chez le chien. D'autres  tudes sont n cessaires afin de confirmer son utilit  clinique.

(Traduit par les auteurs)

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## Introduction

Hypothyroidism is the most commonly diagnosed and misdiagnosed endocrinopathy in dogs (1-15). Hypothyroidism is usually primary and caused by idiopathic atrophy or lymphocytic thyroiditis (1,2,4,6-11,13,14,16-18). The resultant loss of functioning thyroid gland leads to an insufficient production and secretion of thyroid hormones (1,3,4,8,12,17,18). Thyroid hormone deficiency affects multiple metabolic processes of all

body systems. The clinical signs are numerous, variable, often nonspecific, and rarely pathognomonic for hypothyroidism (1,3-5,7,8,11-13,15,17,18). There are many diagnostic tests for assessing thyroid function, but no single test has 100% accuracy (1,4-7,9-11,14-16,18-20). Until recently, the best noninvasive diagnostic test for evaluating thyroid function in dogs was the bovine thyrotropin (bTSH) stimulation test (1,3,5,6,8,12,14,15,18). Unfortunately, bTSH for clinical use is no longer commercially available. A chemical grade of bTSH (Sigma Chemical Company, Oakville, Ontario) is still available, but it is not licensed for clinical use and must be sterilized before administration (6,21). Side effects, including anaphylactoid reactions, associated with the use of chemical grade bTSH preparations for thyrotropin (TSH) stimulation tests in clinical cases have been reported (22).

Recently, another source of pharmaceutical TSH was introduced on the market: recombinant human thyrotropin (rhTSH) (Genzyme Corporation, Cambridge,

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Maine, USA). The rhTSH is a glycoprotein, produced by DNA technology. The intact rhTSH heterodimer is expressed in a line of Chinese hamster ovary (CHO) cells and then purified by a combination of ion exchange and dye affinity chromatography (23–25). The rhTSH produced by the CHO cells presents a different carbohydrate composition than does purified pituitary human TSH (24,26,27). However, the molecular profile of the rhTSH secreted from CHO cells is regarded by some researchers to be more similar to the native protein present in the circulation or in human urine than to human pituitary TSH itself, which is traditionally used for standard preparations (24,26).

The purpose of this study was to evaluate the biological effect of the rhTSH on serum total thyroxine concentrations in euthyroid dogs following its injection by IV, IM, and SC routes.

## Materials and methods

Six healthy beagles, ranging in age from 1 to 2 y, were used. They consisted of 3 neutered males and 3 intact females, weighing between 10 and 16 kg (median, 14 kg). All 3 bitches were in anestrus, based on a physical examination and a serum progesterone concentration. The dogs were euthyroid, based on a complete blood cell count; a biochemical profile; a serum total thyroxine (TT<sub>4</sub>) concentration of over 15 nmol/L, measured by radioimmunoassay (RIA) (Coat-A-Count Canine Total T<sub>4</sub>, Diagnostic Products Corporation, Los Angeles, California, USA); and a basal TSH concentration below 0.7 ng/mL, measured by an immunoradiometric assay (IRMA) (Coat-A-Count Canine IRMA, Diagnostic Products Corporation). The dogs stayed in the kennel where they usually lived for the duration of the experiment. Environmental conditions, such as photoperiod, ventilation, temperature, and humidity, were kept constant throughout the study. Dogs were fed a standard commercial maintenance pellet diet once daily and water was available ad libitum. None of these dogs was receiving any medication. Animal care in this research project was in accordance with the principles and directives of the Canadian Council on Animal Care and was approved by the Ethics Committee of the Faculté de médecine vétérinaire of the Université de Montréal. The study was divided into 3 phases.

**Phase I:** In each of the 6 dogs, TSH response tests were performed at 10-day intervals by using a total dose of 25 µg, 50 µg, and 100 µg of rhTSH (Thyrogen®, Genzyme Corporation), administered IV. Blood samples for measurement of serum TT<sub>4</sub> concentration were taken through an IV catheter at T0, T2, T4, T6, and T8 h.

**Phase II:** In each of the 6 dogs, 10 d after phase I, a TSH response test was performed by using 50 µg of rhTSH, administered IM. Blood samples for measurement of serum TT<sub>4</sub> concentrations, were taken by cephalic venipuncture at T0, T4, T8, T12, T16, T20, and T24 h.

**Phase III:** In each of the 6 dogs, 2 mo after phase II, a TSH response test was performed by using 50 µg of rhTSH, administered SC. Blood samples for measurement of serum TT<sub>4</sub> concentrations, were taken by cephalic venipuncture at T0, T4, T8, T12, T16, T20, T24, T28, T32, and T36 h.

**Table 1. Phase I: Serum TT<sub>4</sub> concentrations (nmol/L) in each dog after IV administration of various doses of rhTSH**

Dog	Time (h)				
	T0	T2	T4	T6	T8
<b>25 µg rhTSH</b>					
1	33.2	46.6	62.4	56.7	40.7
2	32.5	42.4	41.1	34.6	29.1
3	38.5	57.3	58.3	41.2	42.5
4	39.3	51.5	50.7	46.8	36.6
5	40.2	55.1	58.4	57.2	45.6
6	49.9	75.5	70.1	61.3	54.7
<b>50 µg rhTSH</b>					
1	36.5	65.8	64.2	69.4	62.6
2	38.1	48.6	58.9	64.8	54.1
3	32.4	63.7	80.9	74.3	64.5
4	25.7	43.2	39.7	43.8	43.8
5	25.8	40.3	49.9	64.9	38.3
6	34.6	70.3	86.7	78.7	34.4
<b>100 µg rhTSH</b>					
1	22.4	52.6	70.0	75.5	78.2
2	29.9	49.3	61.5	61.6	58.1
3	33.3	53.4	78.6	80.3	87.6
4	12.7	35.8	48.7	59.7	45.9
5	39.6	53.9	64.6	65.7	60.6
6	27.2	70.1	85.5	116.1	97.3

All samples obtained were centrifuged immediately after clot formation and the serum was frozen at  $-20^{\circ}\text{C}$  until assayed. The RIA method cited above was used for all serum TT<sub>4</sub> measurements.

Criteria established to classify dogs as euthyroid following rhTSH administration included either a postTSH TT<sub>4</sub> concentration that increased by at least 24 nmol/L over the basal serum TT<sub>4</sub> value or a postTSH TT<sub>4</sub> concentration that exceeded 45 nmol/L (12,15).

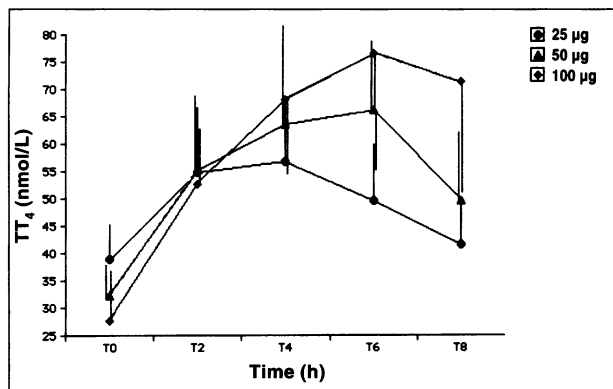
Friedman's nonparametric repeated measures test and Dunn's multiple comparisons test were used for all statistical analyses. A value of  $P < 0.05$  was considered significant. Serum TT<sub>4</sub> concentrations are reported as mean  $\pm$  standard deviation (*s*).

## Results

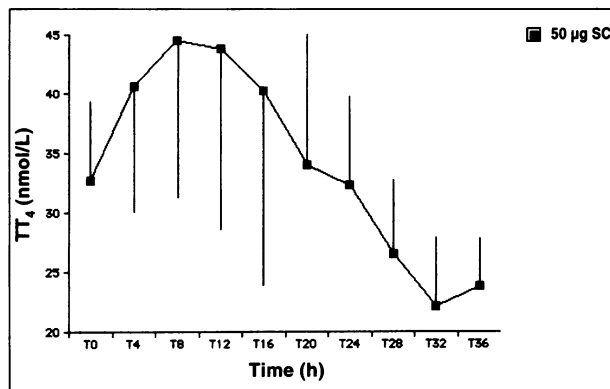
In each phase and following administration of all doses of rhTSH, an increase in serum TT<sub>4</sub> concentration was noted, though this increase was not always significant.

In phase I, following IV administration of 25 µg of rhTSH, there was a significant increase in serum TT<sub>4</sub> concentration at T2 h ( $54.73 \pm 11.55$  nmol/L) ( $P < 0.05$ ) and T4 h ( $56.83 \pm 9.97$  nmol/L) ( $P < 0.01$ ) when compared with T0 h ( $38.93 \pm 6.27$  nmol/L). Two dogs had a postTSH TT<sub>4</sub> increase of at least 24 nmol/L over the basal TT<sub>4</sub> value and 5 dogs had a postTSH TT<sub>4</sub> exceeding 45 nmol/L. Mean serum TT<sub>4</sub> peak concentration was reached at T4 h ( $56.83 \pm 9.97$  nmol/L) (Table 1).

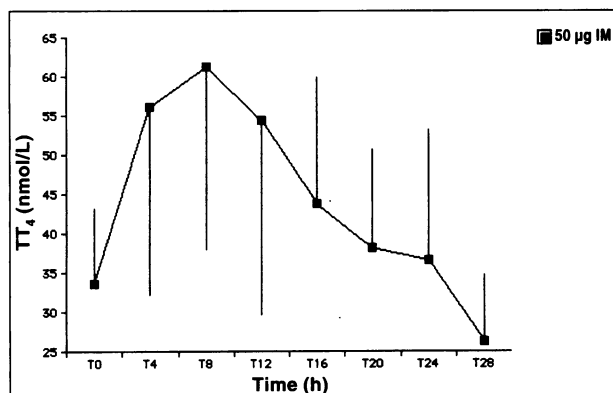
Following IV administration of 50 µg of rhTSH, there was a significant increase in serum TT<sub>4</sub> concentration at T4 h ( $63.38 \pm 17.97$  nmol/L) ( $P < 0.05$ ) and T6 h ( $65.98 \pm 12.14$  nmol/L) ( $P < 0.01$ ) when compared with T0 h ( $32.18 \pm 5.33$  nmol/L). Five dogs had a postTSH TT<sub>4</sub> increase of at least 24 nmol/L over the



**Figure 1.** Mean serum TT<sub>4</sub> concentrations after IV administration of three different doses of rhTSH in 6 euthyroid dogs. Bars represent *s*.



**Figure 3.** Mean serum TT<sub>4</sub> concentrations after SC administration of 50 µg of rhTSH in 6 euthyroid dogs. Bars represent *s*.



**Figure 2.** Mean serum TT<sub>4</sub> concentrations after IM administration of 50 µg of rhTSH in 6 euthyroid dogs. Bars represent *s*.

basal TT<sub>4</sub> value and 5 dogs had a postTSH TT<sub>4</sub> exceeding 45 nmol/L. Mean serum TT<sub>4</sub> peak concentration was reached at T6 h (65.98 ± 12.14 nmol/L) (Table 1).

Following IV administration of 100 µg of rhTSH, there was a significant increase in serum TT<sub>4</sub> concentration at T6 h (76.48 ± 21.00 nmol/L) ( $P < 0.001$ ) and T8 h (71.28 ± 19.61) ( $P < 0.05$ ) when compared with T0 h (27.52 ± 9.28 nmol/L). All dogs had postTSH TT<sub>4</sub> concentrations that increased by at least 24 nmol/L over the basal TT<sub>4</sub> value and that exceeded 45 nmol/L. Mean serum TT<sub>4</sub> peak concentration was reached at T6 h (76.48 ± 21.00 nmol/L) (Table 1; Figure 1).

When comparing the 3 different doses of rhTSH, there was a significant difference between 25 µg and 100 µg at T4 h ( $P < 0.05$ ) and at T6 h and T8 h ( $P < 0.01$ ). No significant difference was noted between doses of 25 µg and 50 µg, or between doses of 50 µg and 100 µg. Considering the statistical results and the criteria established in the beginning of the study to classify dogs as euthyroid following rhTSH administration, 50 µg was judged to be the optimal dose. Thus, for phases II and III of the study, a dose of 50 µg was selected.

In phase II, following IM administration of 50 µg of rhTSH, there was no significant increase in serum TT<sub>4</sub> concentration when compared with baseline serum TT<sub>4</sub> concentration (33.58 ± 10.06 nmol/L). In spite of

statistical results, 5 of the 6 dogs had a postTSH TT<sub>4</sub> increase by at least 24 nmol/L over the basal TT<sub>4</sub> value and 4 dogs had a postTSH TT<sub>4</sub> exceeding 45 nmol/L at one time or another. Mean serum TT<sub>4</sub> peak concentration was reached at T8 h (61.30 ± 23.07 nmol/L) (Figure 2).

In phase III, following SC administration of 50 µg of rhTSH, there was no significant increase in serum TT<sub>4</sub> concentration when compared with baseline serum TT<sub>4</sub> concentration (32.72 ± 6.69 nmol/L). Only 1 dog had a post-TSH TT<sub>4</sub> increase by at least 24 nmol/L over the basal TT<sub>4</sub> value and 2 dogs had a postTSH TT<sub>4</sub> exceeding 45 nmol/L. Serum TT<sub>4</sub> peak concentrations were reached at T4 h in 2 dogs, at T8 h in 1 dog, at T12 h in 2 dogs, and at T24 h in 1 dog after rhTSH administration (Figure 3).

In spite of administration of 5 doses of rhTSH in each dog over a 100-day time period, no side effects or anaphylactic reactions were observed, except for transient pain following the IM injection.

## Discussion

Thyrotropin is the most important regulator of thyroid activity and acts through the initiation of adenosine 3',5'-cyclic phosphate (cAMP) formation and the phosphorylation of protein kinases (33). The TSH molecule is composed of 2 subunits: the alpha (α) subunit is common to many pituitary hormones and is not species specific, the beta (β) subunit is unique for each pituitary hormone and is species specific (18,24). The β subunit provides the biological specificity (24). Even though TSHs from different species have different immunological activities detected via several assays, they share similar biological activity, which explains why the canine thyroid gland responds to bTSH (18). Highly purified rhTSH has been shown to be effective in stimulating cAMP production in rat FRTL5 cells (31). Moreover, it was demonstrated that rhTSH binds to the thyroid TSH receptor in the mouse and rat (34).

In human medicine, rhTSH was approved for use as an adjunctive diagnostic tool for serum thyroglobulin testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer (23,25,29–32). Before the development of the rhTSH, bTSH was utilized. However, the use of bTSH was

abandoned due to a high frequency of allergic reactions, and its repeated use has induced anti-bTSH antibodies that cross-react with human TSH immunoassays. Moreover, these antibodies could neutralize the action of repeated doses of bTSH and bind endogenous human TSH, resulting in the potential for developing secondary hypothyroidism (23,31,32). Therefore, production of bTSH has ceased for human use (32). Human cadaver TSH could also be used, but the risk of transmission of the agent responsible for Creutzfeldt-Jacob disease precludes its clinical use (23,31,32).

In the present study, the results confirmed that the administration of rhTSH has a biological effect on the canine thyroid gland. This is hypothesized to result from rhTSH binding to the canine thyroid TSH receptor and stimulating cAMP production.

Based on data from this study, the administration of 50 µg is judged to be the optimal IV dose of rhTSH for several reasons. First, the increase in serum TT<sub>4</sub> concentration was significant. Second, this increase was also good from a clinical viewpoint (similar to the increase usually obtained with bTSH) (1,6,7,11,12,14). Third, there was no significant difference between rhTSH doses of 50 µg and 100 µg. Finally, the cost of rhTSH could be a limiting factor in a clinical setting.

There are some similarities in results obtained with 50 µg of rhTSH and those obtained with bTSH administered IV in the TSH stimulation test. Peak of post-rhTSH TT<sub>4</sub> concentration was at T6 h; with bTSH, the peak is between T4 h and T8 h. Increases in serum TT<sub>4</sub> concentration are also similar following rhTSH and bTSH administration (1,6,7,11,12,14).

For phases II and III, there was an increase in serum TT<sub>4</sub> concentration after IM and SC administration of rhTSH, but it was not significant. It can be hypothesized that a higher dose of rhTSH would induce a greater stimulation of the thyroid gland. The biological behavior of rhTSH seems to be similar to that of bTSH, thus it can be assumed that the peak of post-rhTSH serum TT<sub>4</sub> concentration with a higher dose of rhTSH would be, as in the TSH stimulation test using bTSH, around 10 and 20 h following IM and SC administration, respectively (7). We suggest that IM and SC are not the most useful routes through which to administer rhTSH, considering the cost involved and the difficulties related to scheduling the procedure.

There is no report on the biologic half-life of TSH in the dog. However, the half-life of human TSH in human is 1 h (17). Thus the time intervals of 10 d between each TSH administration appeared sufficient for a complete elimination of the exogenous TSH and its influence on the hypothalamo-pituitary-thyroid axis in dogs. A period of 2 mo elapsed between phases 2 and 3, because one of the female dogs came into estrus shortly after phase II had been completed.

In human medicine, the use of rhTSH appears safe. Only a few minor adverse effects, such as headache and nausea, have been reported (25,31). No rhTSH antibodies were detected in any patient's serum (25,31). In contrast to bTSH, rhTSH would not induce antibodies to endogenous TSH in humans (23).

Repeated administration of rhTSH in dogs did not induce adverse effects. Though antibody production

against rhTSH was not evaluated, none of the dogs presented any anaphylactic reactions or obvious resistance to rhTSH.

Considering these results, it seems that rhTSH could be a good substitute to bTSH for the TSH stimulation test, when used by the IV route. However, further studies are required to evaluate the optimal dose of rhTSH in hypothyroid dogs, in dogs with nonthyroidal illnesses, and in euthyroid dogs of different sizes receiving or not receiving a medication.

Actual recommendations to assess the canine thyroid function differ from one author to another. Several authors recommend evaluation of serum TT<sub>4</sub> or free T<sub>4</sub> concentration and serum TSH concentration (3,4,20,35); others, recommend as the initial screening, a measurement of serum TT<sub>4</sub>, a complete blood cell count, and a biochemical profile; then, if there is a suspicion of hypothyroidism, a measurement of serum TSH concentration and free T<sub>4</sub> concentration (36). For evaluation of breeding animals, a panel including serum TT<sub>4</sub> and free T<sub>4</sub> concentration, serum TSH concentration, and antithyroglobulin antibody is recommended (36,37). However, in spite of the many diagnostic tools to evaluate the canine thyroid function, several cases may show either discordant or inconclusive results. In these situations, a dynamic function test could help to differentiate a real hypothyroid dog from an euthyroid dog with an impaired thyroid function due to other causes. Moreover, a dynamic function test potentially could help to localize the dysfunction in the hypothalamic-pituitary-thyroid axis (18). Like the TSH stimulation test using bTSH in the past, the TSH stimulation test using rhTSH by the IV route could become a valuable diagnostic tool to assess canine thyroid function when a dynamic function test is required, if the cost were reasonable.

## Acknowledgment

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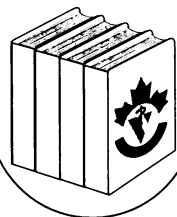
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## BOOK REVIEW



## COMPTE RENDU DE LIVRE

Verstraete FJM. *Self-Assessment Color Review of Veterinary Dentistry*. Iowa State University Press, Iowa, 1999. 228 pp. ISBN 0-8138-2548-2.

Unlike most books, written to impart some knowledge to the reader, this one is designed to test the reader's knowledge of veterinary dentistry. And test one's knowledge it does. There are no chapters or outlines to follow; the questions, written by experts worldwide, are mixed in a random fashion. For orientation, a page of classification gives you the various subjects covered and a detailed index allows you to quickly find a specific

topic. These range from cats and dogs to horses, rabbits, and rodents. Within each species, the various dental disciplines are addressed. Not only does this pocket-book size volume cover a lot of information, it entices the reader to go and learn some more. It is certainly a must for anybody involved in the growing field of veterinary dentistry, be it as a beginner or as a specialist.

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