Evaluation of the Effects of Clomipramine on Canine Thyroid Function Tests

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To evaluate the effect of long-term clomipramine administration on the hypothalamic-pituitary-thyroid axis in healthy dogs, 14 healthy adult dogs were enrolled in a prospective study. Clomipramine (3 mg/kg PO q12h) was administered to all dogs beginning on day 0, and continued for 112 days. Serum total thyroxine (T₄), free thyroxine (fT₄), 3,5,3'-triiodothyronine (T₃), and thyroid-stimulating hormone (TSH) were measured on days 0, 7, 28, 42, 56, and 112. Thyrotropin-releasing hormone (TRH) response tests were performed concurrently. Significant decreases were noted in serum T₄, fT₄, and T₃ concentrations beginning on day 28 through the end of the study period. The lowest mean (±SEM) concentrations of T₄ (26 ± 1.2 to 17 ± 0.5 nmol/L) and fT₄ (1.21 ± 0.13 to 0.83 ± 0.08 nmol/L) occurred at day 112, whereas the lowest mean fT₃ (29 ± 2.4 to 18 ± 1.7 pmol/L) was found on day 56 of clomipramine treatment. The effect of treatment over time on serum T₄ concentration also was significant, but the deviation in T₄ from baseline was variable. No significant effect of clomipramine treatment was noted on either pre- or post-TRH TSH concentrations. The 35 and 38% decreases in serum T₄ and fT₄ concentrations, respectively, during clomipramine administration may lead to a misdiagnosis of hypothyroidism. Although no evidence of hypothyroidism was noted in this study population, subclinical hypothyroidism may have occurred. A longer duration of treatment might further suppress thyroid function, and concurrent illness or other drug administration might exacerbate clomipramine’s effects.

Key words: Dog; Hormone; Thyroxine; Tricyclic antidepressant.

Several drugs have been reported to alter thyroid function tests in dogs, including glucocorticoids, potentiated sulfonamides, and anticonvulsants.14–16 More drugs have been reported to affect thyroid function in humans and other species. Among these, tricyclic antidepressants (TCAs) have been reported to affect thyroid function in humans and other species,9–10 especially selective serotonin reuptake-inhibiting effect by blocking the monoamine reuptake transporter of serotonergic neurons.11,12 Furthermore, the primary metabolite, desmethylclomipramine, is an inhibitor of norepinephrine reuptake.13–15

TCAs have been extensively documented to inhibit thyroid hormone biosynthesis by altering thyroid follicular cell iodine uptake16–18 and inhibiting thyroid peroxidase.17,18 In addition, TCAs interfere with the hypothalamic-pituitary-thyroid (HPT) axis via the serotonergic and noradrenergic systems, and therefore could lead to a decrease in thyroid-stimulating hormone (TSH), thyroxine (T₄), and 3,5,3'-triiodothyronine (T₃) concentrations.

To the authors’ knowledge, no studies on the effect of clomipramine on thyroid function have been performed in the dog. If dogs respond in a manner similar to other species, evaluation of thyroid function tests may result in a misdiagnosis of hypothyroidism if a dog is tested while receiving clomipramine. An additional concern is that if clomipramine decreases plasma thyroid hormones, iatrogenic hypothyroidism may result. This outcome may be of particular concern because hypothyroidism is a contributing factor to a variety of psychologic illnesses in humans, and the therapeutic benefit of TCAs on affective disorders has been positively modulated by thyroid supplementation in both humans9,20 and rats.9 Although the relationship between hypothyroidism and behavioral disorders in dogs is tenuous, aggression has been reported.21,22 Administration of clomipramine, if it induces hypothyroidism, may exacerbate behavioral signs or reduce the potential positive behavioral response to the drug.

The purpose of the study reported here was to evaluate the effect of long-term clomipramine administration on the HPT axis in healthy dogs.

Materials and Methods

Dogs

Fourteen random-source dogs (10 males and 4 neutered females), 16–32 kg in weight, of unknown age were determined to be healthy based on physical examination, CBCs, serum biochemistry, heartworm (Dirofilaria immitis) antigen test, and fecal parasite examination. All subjects were housed in indoor runs with a 12-hour light:dark cycle at 22°C and conditioned for 3 weeks before study. Dogs were fed a maintenance dry food once per day. This protocol was approved by the Virginia Tech University animal care committee, and all animals were cared for according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Euthyroid status was confirmed by finding a normal serum T₄ (>35 nmol/L) response to TSH administration on day −7. The TSH stimulation test23 consisted of measurement of serum T₄ before and 6 hours after administration of bovine TSH at 0.1 IU/kg IV.

Experimental Protocol

Clomipramine (3 mg/kg PO q12h) was administered on days 0 through 112. Dogs acted as their own controls. Blood samples were collected for measurement of serum concentrations of T₄, free thyroxine (fT₄), T₃, 3,5,3'-triiodothyronine (reverse T₃; rT₃), and TSH on days −7, 0, 7, 28, 42, 56, and 112. A thyrotropin-releasing hormone (TRH) stimulation test24 was performed on days 0, 7, 28, 42, 56, and 112 by collecting blood samples for measurement of serum TSH be-
Fig 1. Mean ± SE serum thyroxine (T4) concentration (nmol/L) in 14 dogs treated with clomipramine for 112 days. An asterisk (*) denotes values that are significantly different from those on day 0. The dashed lines denote the reference range.

Fig 2. Mean ± SE serum free thyroxine (fT4) concentration (pmol/L) in 14 dogs treated with clomipramine for 112 days. An asterisk (*) denotes values that are significantly different from those on day 0. The dashed lines denote the reference range.

Fig 3. Mean ± SE serum reverse T3 (rT3) concentration (nmol/L) in 14 dogs treated with clomipramine for 112 days. An asterisk (*) denotes values that are significantly different from those on day 0. The dashed lines denote the reference range.

Statistical Analysis

Statistical analysis was performed by using commercially available software. Repeated measures analysis of variance was applied to test for effects of day of treatment. Covariation among repeated measurements on the same animal were modeled by using a spatial power covariance structure. Significant effects of time on treatment were further investigated by using orthogonal polynomial contrasts, and a P-value < .05 was considered significant.

Results

No adverse effects of the medication or clinical manifestations of hypothyroidism were noted during the treatment period.

A significant (P < .001) effect of treatment time was found on basal T4 concentration (Fig 1). Serum T4 concentration decreased over the treatment course, declining from a pretreatment mean ± SEM of 26 ± 1.2 nmol/L, and reaching a trough of 17 ± 0.5 nmol/L at day 112.

The effect of time on fT4 concentration was significant (P < .0002), with a persistent decrease over the treatment course (Fig 2) from the pretreatment mean of 29 ± 2.4 pmol/L. The lowest mean serum fT4 concentration (18 ± 1.7 pmol/L) was present on day 56, and it remained decreased at 19 ± 1.3 pmol/L on day 112.

A significant (P < .0001) decrease of serum rT3 concentration was found over the study period (Fig 3), from a pretreatment mean of 1.21 ± 0.13 nmol/L to 0.83 ± 0.08 nmol/L on day 112.

The effect of time on serum T3 concentration also was
The synapse is a prolonged process, and weeks are required to reach steady state even though high plasma concentrations are achieved. Power analysis during design of the study determined that a minimum of 12 dogs was required to ensure a type II error of 90% or less. To conserve resources because of the length of the study, all dogs acted as their own controls and were treated with clomipramine.

The results of the present study, which demonstrates that long-term clomipramine administration decreases T₄, fT₄, and rT₃, are consistent with the suppressive effects of TCAs on thyroid function found in other species. Although the effect TCAs have on the thyroid gland and its function varies among species, several mechanisms probably account for the clomipramine-induced depression of thyroid function. Clomipramine binds iodine, thereby preventing T₄ synthesis. Clomipramine’s capacity to donate electrons and impair iodine availability in the thyroid gland has been shown to be 40 times the minimum amount required to produce hypothyroidism, and it has a potency approximately 20% that of methimazole. TCAs also inhibit T₄ production via their effect on thyroid peroxidase (TPO), and in vitro studies have demonstrated that clomipramine irreversibly inhibits TPO by binding iodide molecules to the heme portion of the enzyme. The concentration of clomipramine required for 50% inhibition of horseradish peroxidase (as a substitute for TPO) was approximately 14 times the plasma clomipramine concentration obtained in dogs treated with clomipramine at 2 mg/kg twice daily. However, plasma concentrations are misleading because thyroidal concentrations of imipramine and desipramine (pharmacologically similar TCAs) were 19 and 6 times, respectively, those found in serum in rats treated with these agents for 4 weeks. Therefore, the thyroid gland concentration of clomipramine in dogs in the current study may have been sufficient to inhibit TPO and result in decreases in T₄ and fT₄.

In addition to their effects on thyroid hormone synthesis, TCAs influence T₄ metabolism. In a study of rats treated with desipramine, a TCA similar to clomipramine, an increase in 5'-deiodinase activity (responsible for deiodination of T₄) was noted in the brain. In that study, decreased

**Fig 4.** Mean ± SE serum 3,5,3'-triiodothyronine (T₃) concentration (nmol/L) in 14 dogs treated with clomipramine for 112 days. An asterisk (*) denotes values that are significantly different from those on day 0. The dashed lines denote the reference range.

**Discussion**

The significant decreases in serum concentrations of T₄, fT₄, and rT₃ during clomipramine administration were rapid in onset and consistent throughout the duration of treatment. The lack of a placebo-treated control group in the study detracts from the results because variables other than the effect of clomipramine treatment could have influenced hormone concentrations over time. Thyroid hormone concentrations are known to fluctuate in individual dogs. However, multiple studies over periods of 8 weeks or longer that used similar husbandry conditions have documented little variation in the mean serum T₄ and T₃ concentrations, although fT₄ may be more variable. Similar study designs have been used in other studies that have evaluated the effects of drugs on thyroid function, particularly when the study duration is prolonged. The prolonged duration of treatment in the present study was necessary because the effect of TCA on the monoaminergic systems (serotonin, norepinephrine, and dopamine) via re-uptake inhibition of neurotransmitters at the synaptic cleft may work by modifying receptor site sensitivity rather than by direct action at the receptor site, thereby taking weeks to modulate an effect on serotonin concentrations. This observation is supported by clinical evidence in humans in whom beneficial effects attributable to treatment require 4–6 weeks. Furthermore, negative feedback of the monoaminergic system with resultant upregulation at the level of the synapse is a prolonged process, and weeks are required
The clinical importance of the decrease in \( T_3 \) and \( fT_4 \) with prolonged administration of clomipramine lies in the interference with a diagnosis of hypothyroidism, the potential for hypothyroidism to be induced, and potential effects on the therapeutic response to clomipramine. The reduction of serum \( T_4 \) and \( fT_4 \) concentrations from baseline values by 35 and 38%, respectively, could lead to a misdiagnosis of spontaneous hypothyroidism, and, therefore, thyroid function should be evaluated cautiously in dogs receiving clomipramine.

Although mean concentrations of \( T_4 \) and \( fT_4 \) during clomipramine treatment were within the reference range for most laboratories, examination of our results suggests that clinical hypothyroidism could develop in some circumstances. Dogs with subclinical thyroid dysfunction, those receiving other drugs that suppress thyroid function, and those with nonthyroidal illness could be at risk for developing hypothyroidism during clomipramine administration. Although clinical evidence of hypothyroidism was not found in the present study, subclinical hypothyroidism may have existed. In addition, treatment of longer duration could result in more pronounced effects on thyroid function, and the results of this study should be confirmed in a larger, placebo-controlled population or clinical trial.

Because behavioral changes have been reported in hypothyroid dogs, administration of a TCA such as clomipramine that has the potential to cause hypothyroidism may exacerbate behavioral signs or reduce the benefit of the drug. These phenomena have been investigated in humans, because a decrease in thyroid function has been reported to be associated with depression, and the supplementation of thyroxine or \( T_3 \) as an adjunct to refractory depression has been shown to be beneficial. Although this has not been demonstrated in the dog, and we do not recommend that thyroxine supplementation be administered in refractory cases, it may be prudent to monitor thyroid function tests in addition to conducting a complete physical examination, CBC, and serum biochemistry, before and during clomipramine administration, to ensure that hypothyroidism is not misdiagnosed, or does not subsequently occur.

Footnotes

1. Hill’s Science Diet Maintenance (Dry), Hill’s Corporation, Topeka, KS
2. bovine TSH, Sigma Chemical Corporation, St Louis, MO
3. Clomicalm, Novartis Animal Health, Greensboro, NC
4. pGlu-His-Pro-amide trifluoroacetate salt (Synthetic TRH), Sigma Chemical Corporation, St Louis, MO
5. Coat-A-Count Canine TSH IRMA, Diagnostic Products Corporation, Los Angeles, CA
6. Coat-A-Count Canine T\(_4\), Diagnostic Products Corporation, Los Angeles, CA
7. Coat-A-Count Canine T\(_3\), Diagnostic Products Corporation, Los Angeles, CA
8. Reverse T, Radioimmunoassay, Biochim Immunysystems Italia SPA, Bologna, Italy
9. Free T\(_4\) by Equilibrium Dialysis, Nichols Diagnostics, San Luis Obispo, CA
10. SAS, version 6.12, SAS Institute, Cary, NC

Acknowledgments

We wish to thank Dan Ward for support with statistical analysis; John Strauss, Taryn Brandt, and Stephanie Milburn for assistance with data collection; and Novartis An-
nimal Health for donation of the clomipramine. This research was supported by a grant from the Virginia Veterinary Medical Association.

References

39. Rousseau A, Marquet P, Lagorce JF, et al. Thyroid accumulation and adverse effects of imipramine and desipramine in rats after long-
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