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Effects of Carpofen and Chondroitin Sulphate in Thyroid Function Tests in Dogs with Musculoskeletal

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Abstract: Several non-thyroid factors such as age, breed, concomitant diseases and use of certain drugs might influence the diagnosis of hypothyroidism in dogs. Changes in the concentrations of thyroid hormones due to non-thyroid illnesses or drugs are named euthyroid sick syndrome. The aim of this study is to evaluate the thyroid function in dogs with musculoskeletal diseases or without musculoskeletal diseases receiving carprofen and chondroitin sulphate, glucosamine, collagen, ascorbic acid and manganese sulphate. A total of 43 dogs were used, divided into three groups: 20 dogs in the Carprofen Group (GC), 20 dogs in the Chondroitin Sulphate Group (GSC) and 15 dogs in the placebo group (GP). The animals included in the GC group were previously diagnosed with degenerative joint disease. Dogs in the GSC and GP groups did not present joint diseases or a diagnosis of systemic disease. Dogs in the GC group received daily 2.2 mg kg^{-1} carprofen during 60 days, twice a day. The dogs in the GSC group received daily chondroitin sulphate (30 mg kg^{-1}) and association (glucosamine, collagen, ascorbic acid, manganese sulphate) during 60 days, twice a day. Dogs in the GP group received daily 10 mg kg^{-1} corn starch in capsule during 60 days, twice a day. The animals were evaluated in five Moments (M), the initial Moment (M0), before the first administration, resulting in basal values within the parameters studied; at 15 days (M1), at 30 days (M2), at 45 days (M3) and at 60 days (M4). The measurements of thyroid function (total thyroxine-TT4, free thyroxine-FT4, thyrotropin-TSH) were performed in the five moments. In the control group the M's had an effect on TT4 and FT4 with reduced concentrations of TT4 below the reference values. In the SC group, the M's had an effect only on the FT4 and the highest average was observed in M4. Carprofen in dose for 60 days promoted the reduction of serum TT4 in dogs with musculoskeletal diseases. Therefore, the strain caused the TT4 would be consistent with hypothyroidism. Recommend discontinuation of therapy with carprofen for a minimum period of 15-30 days before the tests of thyroid function to be interference. While chondroitin sulfate at the dose and duration used does not alter thyroid function.

Key words: Euthyroid, non-thyroid illnesses, hypthyroidism, AINES, FT4

INTRODUCTION

Several non thyroid factors, such as age, breed, concomitant diseases and administration of certain drugs can influence the diagnostic of hypothyroidism in dogs (Ferguson, 1997). There are drugs that affect both thyroid function tests and the dog's gland itself. Thus, knowledge of those that alter the concentration of thyroid hormones or that elevate the serum Thyroid-Stimulating Hormone (TSH) aids towards a correct interpretation of test results. Glucocorticoids, sulphonamides, Non-Steroid Anti-Inflammatory Drugs (NSAIDs) and phenobarbital are a few of the drugs known to affect the Hypothalamus-Hypophysis-Thyroid (H-H-T) axis.

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Therefore, the results of thyroid function tests must be carefully evaluated in patients under therapy and/or extensive therapy with these drugs (Hall *et al*., 1993; Gaskill *et al*., 1999; Gulikers and Panciera, 2002; Daminet and Ferguson, 2003). Nonetheless, while this relationship has not been established in dogs, the interpretation of thyroid function tests must be made with care regarding the usage of specific drugs.

Changes in the concentration of thyroid hormones due to Non-Thyroid Illnesses (NTIs) are well-known in humans and animals. NTI is also known as the Euthyroid Sick Syndrome (ESS). In humans, it decreases the concentration of Total Triiodothyronine (TT3) while serum concentrations of Total Thyroxin (TT4) remain within normal limits. However, in severe diseases, a reduction in TT3 and TT4 can occur. But in these cases, the free portion of hormones remains within normal levels (Mooney *et al*., 2008). Nevertheless, in dogs, the reduction of only TT3 concentrations is uncommon. Most of the time, there is a reduction in TT3 and TT4 and in some cases, only in TT4. While Free Thyroxin (FT4) is less affected by NTIs in severe systemic diseases, the decrease is mild (Kantrowitz *et al*., 2001).

Considering the intricate H-H-T axis, several drugs can induce changes in the concentration of thyroid hormones which can pose complications to the evaluation of tests and even lead to a misdiagnosis of hypothyroidism. Misdiagnosis can result in wrong treatment and in harmful effects to the patient. The results of clinical and pathological tests and the concentrations of thyroid hormones is to be interpreted together with clinical history and with compatible findings in physical examination (Daminet and Ferguson, 2003).

The aim of this study is to evaluate the thyroid function in dogs with musculoskeletal diseases or without musculoskeletal diseases receiving carprofen and chondroitin sulphate, glucosamine, collagen, ascorbic acid and manganese sulphate.

MATERIALS AND METHODS

The study was carried in dogs presented to three veterinary centers in the state of Parana, being two veterinary hospitals and one private clinic in the period of 12 months. The selection of animals for the study was performed by Veterinarians and the inclusion in each group was made in a random manner.

Animals: A total of 55 dogs were used, divided into three groups: 20 dogs in the Carprofen Group (GC), 20 dogs in the Chondroitin Sulphate Group (GSC) and 15 dogs in the Placebo Group (GP). But, only 43 animals remained until the end of the study. The dogs were aged between 2 and 10 years, being 24 male and 31 female, weighing between 12 and 23 kg. All dogs were submitted to screening tests including CBC, urea, creatinine, urinalysis, alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP) and only those presenting laboratory tests within reference values for the species were included in the study.The animals included in the GC group were previously diagnosed with degenerative joint disease. Dogs in the GSC and GP groups did not present joint diseases or a diagnosis of systemic disease.

Dogs in the GC group received daily 2.2 mg kg^{-1} carprofen (Carprodyl®, Ceva SanteAnimale, Brasil) during 60 days, twice a day. The dogs in the GSC group received daily chondroitin sulphate 200 mg (30 mg kg^{-1}), glucosamine 300 mg, collagen 50 mg, ascorbic acid 50 mg and manganese sulphate (Condroton®, Vetnil, Brasil) during 60 days, twice a day. Dogs in the GP group received daily 10 mg kg^{-1} corn starch in capsule during 60 days, twice a day.

The animals were evaluated in five Moments (M), the initial Moment (M0), before the first administration, resulting in basal values within the parameters studied; at 15 days (M1), at 30 days (M2), at 45 days (M3) and at 60 days (M4).

Analytical method: Blood was collected in the morning with the animals on an empty stomach. Blood samples were collected from the jugular vein in tubes containing clot activator gel. The tubes were centrifuged at 2000 g for 10 min in <1 h after collection. After serum separation, the samples were aliquoted and frozen in Freezer at -70° C. The measurements of thyroid function, hepatic enzymes, urea, creatinine, total protein and albumin were performed in the five moments.

Total T4 was measured by use of a commercially a vailable solid-phase radioimmunoassay kit (Clinical Assays Gammacoat M Total T4 RIA Kit; DiaSorin Inc., Still water, MN, USA) that has been validated for canineserum. Free T4 wasmeasuredby use of a commercially available kit (Free T4 by equilibrium dialysis; Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) that has been validated in that laboratory for canineserum. Canine TSH was measured by use of a commercially available immunoradio metricassay (Coat-A-Countcanine TSH IRMA; Diagnostic Products Corp., Los Angeles, CA, USA) that has been validated in that laboratory for canineserum. Normal values for Thyroid-Stimulating Hormone (TSH) were 0.18-1 ng dL^{-1}, for TT4 1.5-4 ug dL^{-1} and for FT4 1.0-4.0 ng dL^{-1}.

Statical analysis: The experimental design was entirely randomized, weighing the effect of Leishmaniasis on the variables TSH, TT4 and FT4. Variance analysis weighed the effect of these groups on the concentrations of TSH, TT4 and FT4. All variables were previously submitted to Lilliefors and Levene tests. Distributions that did not present variance homogeneity but presented $p<0.05$ in the variance analysis had means compared by Scheffe test which is more robust in face of violations in variance equalities. All analyses were performed in Statica 7.0 program for Windows® (SPSS, USA).

RESULTS AND DISCUSSION

A total of 43 dogs remained until the end of the study, divided into three groups: 15 dogs in the Carprofen Group (GC), 17 dogs in the Chondroitin Sulphate Group (GSC) and 11 dogs in the Placebo Group (GP). Three animals in the GC group presented vomit and gastritis during the study, one developed chronical kidney disease and one owner gave up treatment. In the GSC group, one was excluded due to ehrlichiosis and two had their therapies discontinued by the owners. In the GP group, one was excluded due to vomit, one due to bronchopneumonia, one due to diarrhea and two discontinued the therapy by the owners.

The was an increase in the activity of hepatic enzymes (ALT, ALP) in three dogs in the GC group, two in the GSC group and one in the GP group. However, there were no significant differences among the moments. No alterations in the serum values of urea, creatinine and albumin were observed in the different moments studied, in the three groups.

Carprofen: In the GC group, the variance analysis showed that the Ms had effect on TT4 and FT4 ($p<0.05$). The mean value for TT4 was higher in M0 (2.36). In M1, the mean value was lower when compared to M0, at 1.68. Lower values of TT4 occurred in M2, M3 and M4, despite not presenting any difference among each other. The FT4 values did not differ among Ms according to Tukey test, presenting great variations, mainly in M2, a fact that aids the lack of statistic differences (Table 1). In M2, M3 and M4, TT4 serum values were below reference values.

Chondroitin sulphate: In the SC group, Ms had effect only on FT4 and the greatest mean ($p<0.05$) was observed in M4 (1.74). In M0, M1, M2, M3 and M4, FT4 means were lower when compared to M4, despite not presenting differences among each other (Table 2). In M4, there was an increase in the concentration of FT4 with statistic difference. However, the values remained within the normal values for the species.

Placebo: In the GP group, Ms had effect on FT4, being that M1 had the lowest mean ($p<0.05$) in relation to M0, M3 and M4. On the other hand, FT4 mean value in M2 did not differ from the other Ms (Table 3). However, the values remained within the normal values for the species.

The non-thyroid illness and the administration of drugs such as phenobarbital sulfonamide and glucocorticoids, can decrease TT4 and TT3 concentrations. The combination of low values of thyroid hormones and non-thyroid diseases are refered as euthyroid disease syndrome or non-thyroid disease syndrome (Piechotta *et al*., 2012).

The stress induced by non-thyroid illnesses can cause increase in the circulation of glucocorticoids and

Table 1: Mean ($\bar{x}$) Standard Deviation (SD), Standard error (S) and range for TSH, TT4, FT4 and protein at different Ms for 15 dogs receiving carprofen

Parameters	References	TSH p = 0.07 (0.18-1 ng mL^{-1})	TT4 p<0.01 (1.5-4.0 ug dL^{-1})	FT4 p<0.01 (1.0-4.0 ng dL^{-1})	Protein p = 0.45
M0	Mean±SD(s)	0.44±0.24 (0.061)	2.36^{a}±0.84 (0.217)	2.20^{a}±0,15 (0.039)	7.68±0.46(0.118)
	Range	0.16±0.87	1.08±3.84	2.02±2.46	6.90±8.40
M1	Mean±SD(s)	0.68±0.68 (0.072)	1.68^{b}±0.50 (0.128)	1.85^{b}±0.46 (0.119)	7.39±0.40(0.102)
	Range	0.23±1.10	0.93±2.55	1.13±2.36	6.80±8.10
M2	Mean±SD(s)	0.57±0.28 (0.072)	0.69^{c}±0.19 (0.049)	2.36^{a}±2.81 (0.706)	7.27±0.66(0.167)
	Range	0.14±1.00	0.29±0.93	0.89±1.20	5.60±8.10
M3	Mean±SD(s)	0.61±0.37 (0.096)	0.70^{c}±0.24 (0.062)	1.28^{b}±0.27 (0.069)	7.05±0.50(0.128)
	Range	0.18±1.19	0.29±1.06	0.95±2.00	6.50±8.00
M4	Mean±SD(s)	0.61±0.35(0.091)	0.68^{c}±0.22 (0.056)	1.13^{b}±0.15 (0.039)	7.15±0.44(0.113)
	Range	0.18±1.20	0.34±0.94	0.80±1.30	6.70±8.10

Means followed by equal letters under same column did not differ in Tukey test ($p>0.05$); n = number; Total Thyroxine (TT4); Free Thyroxine (FT4); Thyrotropin (TSH)

Table 2: Mean ($\bar{x}$) Standard Deviation (SD), Standard error (S) and range for TSH, TT4, FT4 and protein at different Ms for 17 dogs receiving chondroitin sulphate and asscoiation

Parameters	References	TSH p = 0.07 (0.18-1 ng mL^{-1})	TT4 p<0.01 (1.5-4.0 ug dL^{-1})	FT4 p<0.01 (1.0-4.0 ng dL^{-1})	Protein p = 0.45
M0	Mean±SD(s)	0.41±0.23 (0.057)	1.99±0.78 (0.189)	1.29^{a}±0.30 (0.074)	7.06±0.74(0.179)
	Range	0.13±0.94	0.67±3.96	1.01±1.98	5.60±8.10
M1	Mean±SD(S)	0.59±0.35 (0.084)	2.11±0.94 (0.228)	1.19^{a}±0.19 (0.046)	7.40±0.41 (0.099)
	Range	0.18±1.20	1.14±4.37	1.02±1.68	6.60±8.00
M2	Mean±SD(S)	0.69±0.32 (0.77)	1.90±0.77 (0.186)	1.08^{a}±0.30 (0.074)	7.41±0.66(0.161)

Table 2: Continue

Parameters	References	TSH p = 0.07 (0.18-1 ng mL^{-1})	TT4 p<0.01 (1.5-4.0 ug dL^{-1})	FT4 p<0.01 (1.0-4.0 ng dL^{-1})	Protein p = 0.45
	Range	0.18±1.20	0.81±3.50	0.39±1.68	6.60±8.60
M3	Mean±SD(S)	0.67±0.29 (0.072)	1.38±0.72 (0.179)	1.20^{a}±0.21 (0.052)	7.57±0.65(0.163)
	Range	0.23±1.14	0.46±2.55	0.89±1.64	6.0±8.50
M4	Mean±SD(S)	0.64±0.37 (0.093)	2.07±1.06 (0.264)	1.74^{b}±0.53 (0.133)	7.51±0.67(0.168)
	Range	0.20±1.20	0.73±3.78	1.03±2.46	6.80±8.50

Table 3: Mean ($\bar{x}$), Standard Deviation (SD), Standard error (S) and range for TSH, TT4, FT4 and protein at different Ms for 11 dogs receiving plcebo

Parameters	References	TSH p = 0.07 (0.18-1 ng mL^{-1})	TT4 p<0.01 (1.5-4.0 ug dL^{-1})	FT4 p<0.01 (1.0-4.0 ng dL^{-1})	Protein p = 0.45
M0	Mean±SD(s)	0.44±0.25 (0.076)	2.73±0.64 (0.193)	2.22^{a}±0.16 (0.047)	7.56±0.46(0.139)
	Range	0.16±0.87	2.02±2.46	1.96±3.84	6.90±8.40
M1	Mean±SD(s)	0.45±0.28 (0.079)	2.36±0.64 (0.178)	1.37^{b}±0.41 (0.112)	6.92±0.67(0.186)
	Range	0.13±0.94	1.01±2.33	1.62±3.96	5.60±8.00
M2	Mean±SD(s)	0.82±0.36 (0.113)	2.67±0.86 (0.27)	1.76^{ab}±0.56 (0.177)	7.65±0.70(0.222)
	Range	0.20±1.20	1.40±3.78	1.05±2.46	6.80±8.50
M3	Mean±SD(s)	0.44±0.27 (0.082)	2.70±0.71 (0.214)	1.99^{a}±0.39 (0.117)	7.16±0.43(0.131)
	Range	0.13±0.94	1.36±2.46	1.65±3.96	6.60±7.90
M4	Mean±SD(s)	0.46±0.29 (0.08)	2.64±0.67 (0.186)	1.95^{a}±0.44 (0.122)	7.12±0.41(0.115)
	Range	0.13±0.94	1.11±2.46	1.65±3.96	6.60±7.90

Means followed by equal letters under the same column did not differ in Tukey test (p>0.05); n = number; Total Thyroxine (TT4); Free Thyroxine (FT4); Thyrotropin (TSH)

alter thyroid function (Scott-Moncrieff *et al*., 1998; Kooistra *et al*., 2000). Chronic pain induced by osteoarthritis can promote stress and alter thyroid function. However, apparently, severe chronic osteoarthritis does not cause alterations to the thyroid function in dogs (Paradis *et al*., 2003). Therefore, it is necessary to evaluate the influence of NSAIDs in chronic joint diseases, since both could alter the thyroid function. In this study, the thyroid function was evaluated, without evaluating the concomitant influence of stress from chronic disease and drugs.

The NSAIDs cause alterations to thyroid function tests, mainly by changes in the thyroid hormone bonds to plasma transport proteins (Gulikers and Panciera, 2002; Panciera and Johnston, 2002). Dogs included in GC presented a decrease in TT4 serum concentrations below reference values for healthy dogs (Feldman and Nelson, 2004) and discrete elevation in TSH concentrations. However, there was a reduction in FT4 serum concentrations in M1 and elevation in M2 (30 days of carprofen) followed by a decrease in M3 and M4. These results can be explained by the high binding to proteins that the circulating thyroid hormones present and, some NSAIDs can displace them from their binding sites to the serum proteins, resulting in a transitory increase in FT4 serum concentration (Gulikers and Panciera, 2002).

These results differ from prior studies performed with the use of carprofen. The use of carprofen in the dosage of 2.2-3.3 mg kg^{-1} twice a day for 5 weeks decreased TSH concentrations (Ferguson, 1997). However in a study by Sauve *et al*. (2003) where carprofen was used in the dosage of 1.7-2.3 mg kg^{-1} day during 60 days, there were no changes to the thyroid function.

The increase in FT4 concentration is used as negative feedback in hypothalamus and hypophysis, decreasing TSH secretion and finally resulting in the decrease of T4 serum concentration, regardless of the normal FT4 concentration (Gulikers and Panciera, 2002). The decrease in serum TSH concentration occurred together with the elevation of FT4; however, it only took place at M2 (14 days) without significant differences. These animals continued euthyroid but the alteration in the test results could lead to the misdiagnosis of hypothyroidism, since there was a reduction in TT4 showing that TT4 can not be used as the only test to evaluate dogs receiving NSAIDs. Also, the deionization of thyroid hormones can also be mildly decreased in dogs receiving NSAIDs, since, it harms the 5'-deiodinase function (Gulikers and Panciera, 2002). As there were no measurement of TT3 and rT3, it was not possible to evaluate the influence of carprofen in deionization.

The discrete reduction in TSH could have contributed to the decrease in TT4 serum concentrations. TT4 serum values were below reference values after the use of carprofen. Similar findings were described in dogs receiving deracoxib, acetylsalicylic acid (ASA), phenobarbital and also carprofen (Daminet *et al*., 2003; Panciera *et al*., 2006).

According to Fitzgerald and Patrono, the use of deracoxib can result in a decrease in T4 and T3 serum

concentrations due to its high binding to proteins. However, Panciera *et al.* (2006) did not observe variation in thyroid functiontestsin dogs receiving deracoxib in the dosage of 1.25-1.8 mg kg^{-1} during 28 days. In the same study, a decrease in TT4, TT3 and FT4 concentrations was observed with the use of aspirin in the dosage of 75 mg kg^{-1} As well as the displacement of thebinding sitesin plasma proteins caused by ASA, dosage and duration of treatment could have contributed to these results.

Carprofen in the usage dose, during 60 days, promoted the decrease in TT4 serum concentrations in dogs with musculoskeletal diseases. Therefore, the isolated use of TT4 in the evaluation of thyroid function in these animals would be compatible to hypothyroidism. It is recommended to interrupt the therapy with carprofen for a minimum period of 15-30 days before the thyroid function tests are performed in order to avoid interference in the results.

The dogs in the GSC group did not present significant difference in the values of thyroid hormones. Similar results had been described by Sauve *et al.* (2003). A significant increase in FT4 concentrations was observed in M4 in relation to M3. However, the values continued within the normal standards for the species (Feldman and Nelson, 2004). This difference was due to the variation >100% in the concentrations of one of the dogs studied. However, it was not possible to determine the reason of this variation in the animal. Therefore, in the dosage and period used, chondroitin sulphate does not alter thyroid function.

The dogs in the GP group presented variations in the FT4 values with a decrease in M1 and higher elevation, without difference, only in M2. However, the values continued within the normal range for the species. This reduction was due to the decrease in FT4 concentrations in one of the dogs studied. It was not possible to establish the cause for this reduction but it was probably due to the circadian variation, the environment where the dog lives whether internal or outdoors and seasonal variation that could have influenced the results. The environmental factor might be the one that most contributed to the FT4 variation, both in the placebo group and the chondroitin sulphate group, since the animals were kept at their owner's houses. That fact did not provide an equal and controlled environment among all animals in the study.

Environmental factors such as temperature and seasonality can lead to the development of ESS. Large, medium and small-size dogs kept in external environments present higher FT4 concentrations in comparison to dogs kept in internal environments, since this variation is significant and dependent on the environmental temperature (negative correlation with environmental temperature). Moreover, TT4 and FT4 serum concentrations present seasonal variation. Other factors that also influence the serum concentrations of thyroid hormones are latitude, circadian rhythm and also seasonal changes (Hoh and Oh, 2006; Reynolds *et al.*, 2008).

Circadian rhythm has probably not influenced the concentrations, since the collections were always performed at the same time. Other factors such as age, gender, breed, infectious diseases, temperature and seasonality might have contributed to these changes in thyroid concentrations (Ferguson, 1997; Ferm *et al.*, 2009; Fialkovicova *et al.*, 2012).

Environmental temperature could have influenced the concentrations in GP and GSC, since climate variation significantly alters FT4 concentrations by promoting changes in basal metabolic rate. However, the environmental temperature variation was not evaluated throughout this study.

CONCLUSION

Carprofen in the usage dose, during 60 days, promoted a decrease in TT4 serum concentrations in dogs with musculoskeletal diseases. Therefore for TT4 it must not be used in isolation to evaluate thyroid function. Chondroitin sulphate in the dosage and timeframe used does not interfere in thyroid function for study.

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