Influence of Various Medications on Canine Thyroid Function

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ABSTRACT: Many drugs alter thyroid function tests, and some cause clinical hypothyroidism. Sulfonamides are probably the most potent antithyroid drugs commonly used, and administration at a high dose for a prolonged period can result in hypothyroidism. Glucocorticoids, phenobarbital, and clomipramine are other commonly used drugs that alter thyroid function tests and may lead to a misdiagnosis of spontaneous hypothyroidism. NSAIDs, radiographic contrast agents, and amiodarone are among the drugs that have been shown to alter thyroid function in dogs. Caution should be exercised when interpreting thyroid function tests in dogs receiving any of these agents.

Assessment of thyroid function in dogs can be complicated by several factors. First, hypothyroidism results in clinical signs that are often vague. In addition, no single thyroid function test is completely reliable. Decreased serum total thyroxine (T4) concentration appears to be a highly sensitive (0.89) test for hypothyroidism but has a lower specificity (0.82). When measured by equilibrium dialysis, serum-free thyroxine (fT4) concentration is more specific (0.93) than total T4 but can be altered by certain nonthyroidal influences. The serum thyrotropin (thyroid-stimulating hormone [TSH]) assay has been less accurate than the aforementioned tests of thyroid function, with a sensitivity that ranges from 0.63 to 0.87 (up to 37% false negative) and a specificity of 0.82 to 0.93 (up to 18% false positive). Measurement of serum triiodothyronine (T3) concentrations is rarely of use clinically because up to 90% of hypothyroid dogs have a normal serum T3.

Finally, other factors, such as the administration of drugs or the presence of systemic disease (i.e., nonthyroidal illness syndrome, also called euthyroid sick syndrome), can markedly affect thyroid function and thyroid function tests. Drugs are known to affect thyroid function at all levels of the hypothalamic–pituitary–thyroid (HPT) axis. A basic knowledge of thyroid hormone synthesis and the HPT axis is essential for understanding the effects of various drugs.
**THYROID PHYSIOLOGY**

Thyroid hormone synthesis begins with absorption of dietary iodide, which is then transported in plasma to the thyroid (Figure 1). Organification of iodide occurs in the thyroid gland where it is oxidized by thyroid peroxidase to form iodine, which binds to tyrosine residues on the thyroglobulin molecule. This results in the production of mono- and diiodotyrosine, which ultimately undergo a coupling reaction catalyzed by thyroid peroxidase to form T₄ or T₃ on thyroglobulin. Secretion occurs when colloid, containing thyroglobulin, is taken from the follicular lumen by endocytosis. In the thyroid cell, the thyroglobulin undergoes proteolysis in a phagolysosome to release T₄ and T₃, which are then secreted when the phagolysosome fuses with the cell membrane. The ratio of T₄:T₃ secreted by the canine thyroid gland is 4:1. In hypothyroid animals, this ratio decreases when the thyroid gland undergoes stimulation by TSH as T₃ is preferentially released to maintain serum concentrations.

Synthesis and secretion of thyroid hormones are controlled by a complex negative feedback system that originates in the hypothalamus with the production of thyrotropin-releasing hormone (TRH). This compound is secreted into the hypophyseal portal system from the paraventricular nucleus of the hypothalamus and has a direct stimulatory effect on secretion of TSH from the anterior pituitary (Figure 2). TSH, which is produced by thyrotropes in the anterior pituitary, stimulates T₄ synthesis and secretion by the thyroid gland. Thyrotrope secretion of TSH is under direct negative feedback regulation by circulating thyroid hormone levels. The sensitivity of this feedback is modulated by TRH. Additionally, glucocorticoids, growth hormone, somatostatin, dopamine, and androgens have also been shown to decrease TSH secretion.

Once released into the plasma, T₄ and T₃ are immediately bound by a number of plasma proteins, including thyroxine-binding globulin, thyroxine-binding prealbumin, and albumin. Approximately 99.9% of T₄ is bound to plasma proteins. Only the unbound (or free) portion leaves the circulation to exert the cellular effects of thyroid hormones. Although T₄ is the main secretory product of the thyroid gland, T₃ is more effective in binding to and activating thyroid hormone receptors in the cell nucleus. The peripheral tissues (e.g., liver, kidneys) deiodinate T₄ to form T₃ (5'-deiodination) or the metabolically inactive reverse T₃ (rT₃; 5-deiodination). In addition, thyroid hormones undergo glucuronidation (in the liver and kidneys) and sulfation (via hepatic phenosulfotransferases) to be excreted by the biliary system or in urine.

Given the intricacy of the HPT axis, drug-induced alteration of thyroid hormone concentrations can be perplexing and may lead to an erroneous diagnosis of hypothyroidism. A misdiagnosis could result in subsequent inappropriate treatment and deleterious effects to the patient. Numerous drugs have been reported to...
alter thyroid function in both rats and humans by modifying the synthesis, secretion, transport, or metabolism of thyroid hormones. Furthermore, some medications may inhibit the HPT axis. Drug-induced antithyroid effects vary among species, but medications known to alter thyroid function that are frequently used in dogs include phenobarbital, glucocorticoids, NSAIDs, and sulfonamides. Table 1 provides a summary of the various medications that affect thyroid function, classified by their mechanism of action. Unfortunately, the antithyroid consequences of many of these drugs have not been tested in dogs. The differences between rodent, human, and canine thyroid physiology make it impossible to extrapolate from one species to another. As veterinary medicine becomes more sophisticated, an ever-increasing number of drugs that alter thyroid function in other species are being used in dogs, and the potential effects of pharmaceuticals on thyroid function should be considered when interpreting thyroid function tests.

### SULFONAMIDES

Although the exact mechanism of sulfonamides on thyroid function is poorly understood, it is surmised that they act by inhibiting thyroid peroxidase. Because thyroid peroxidase mediates iodide organification and the coupling reaction to form T₄ and T₃ on thyroglobulin, the result of its inhibition is decreased serum thyroid hormone secretion. Pituitary thyrotropes respond to the decrease in thyroid hormones via reduced negative feedback inhibition, which results in increased pituitary secretion of TSH.

Studies in humans show only mild decreases of thyroid function during treatment with sulfonamides, in contrast to the severe thyroid dysfunction induced in rats. Several prospective studies have evaluated the effects of sulfonamide administration on canine thyroid function. In a controlled study, trimethoprim–sulfadiazine (15 mg/kg PO q12h) administered to normal dogs over 4 weeks had no significant effect on T₄, T₃, and fT₄ serum concentrations or the serum T₄ response to TSH administration. In contrast, trimethoprim–sulfamethoxazole (30 mg/kg PO q12h) administered to dogs with pyoderma for 6 weeks resulted in significantly decreased T₄ and T₃ concentrations and subsequently increased TSH levels. These studies indicate that the effects of sulfonamides on thyroid function are dose and time dependent, but the various sulfamoyl moieties used
could also influence thyroid hormone concentrations.

Sulfonamides not only alter thyroid function test results but can ultimately lead to clinical hypothyroidism in some patients. Thyroid function tests in these dogs are indistinguishable from those patients with spontaneous hypothyroidism. If available, nuclear scintigraphy of the thyroid can aid in distinguishing endogenous versus sulfonamide-induced hypothyroidism. Because sulfonamides do not inhibit iodide uptake, thyroid gland uptake of pertechnetate should be normal to increased in dogs with sulfonamide-induced hypothyroidism. Conversely, pertechnetate uptake would be reduced in dogs with spontaneous primary hypothyroidism caused by lymphocytic thyroiditis or idiopathic thyroid atrophy. Thyroid scintigraphy is rarely indicated when sulfonamide-induced hypothyroidism is suspected. The associated clinical signs and depressed thyroid hormone levels from sulfonamide-induced hypothyroidism gradually resolve once sulfonamide administration is ceased. Normalization of thyroid function tests after cessation of sulfonamide administration has taken up to 12 weeks but may occur in as little as 1 week.

It appears that the effects of sulfonamides on thyroid function occur primarily at high doses (exceeding 30 mg/kg/day of potentiated sulfonamide) when given for 4 weeks or more. When given at doses recommended by the manufacturer (15 mg/kg PO q12h) for treatment of urinary tract and other infections for 4 weeks or less, administration of sulfadiazine and trimethoprim in combination does not affect thyroid function tests in dogs (although this dose was evaluated in only one study). If prolonged use results in clinical signs suggestive of hypothyroidism, discontinuation of the drug may result in normalization of T₄ concentrations in as few as 7 days, and levothyroxine supplementation should not be necessary during this short period. Failure to consider the effects of sulfonamides on thyroid function tests could lead to an inappropriate diagnosis of hypothyroidism.

### Table 1. Partial List of Medications That Affect Thyroid Hormones in Humans and Dogs

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Medications Affecting Humans</th>
<th>Medications Affecting Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased TSH secretion</td>
<td>Cyproheptadine, dopamine, glucocorticoids, octreotide, sulfonamides, thyroxine supplementation, tricyclic antidepressants</td>
<td>Glucocorticoids, sulfonamides, thyroxine supplementation, tricyclic antidepressants</td>
</tr>
<tr>
<td>Increased thyroid hormone secretion</td>
<td>Amiodarone, iodide</td>
<td>Amiodarone, iodide</td>
</tr>
<tr>
<td>Decreased thyroid hormone secretion</td>
<td>Amiodarone, aminogluthethimide, calcium-channel blockers, iodide, lithium, radiocontrast agents (e.g., ipodate), thioamides, tricyclic antidepressants</td>
<td>Amiodarone, iodide, radiocontrast agents (e.g., ipodate), tricyclic antidepressants</td>
</tr>
<tr>
<td>Decreased T₄ absorption (patients on supplementation)</td>
<td>Aluminum hydroxide, ferrous sulfate, sucralfate</td>
<td>None</td>
</tr>
<tr>
<td>Altered serum transport via increased T₃-binding globulin concentration</td>
<td>Estrogens, mitotane, tamoxifen</td>
<td>None</td>
</tr>
<tr>
<td>Altered serum transport via decreased T₃-binding globulin concentration</td>
<td>Androgens, L-asparaginase, glucocorticoids</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Displacement from plasma-binding proteins</td>
<td>Furosemide, heparin, NSAIDs (e.g., salicylates), phenylbutazone, radiocontrast agents (e.g., ipodate)</td>
<td>Furosemide, glucocorticoids, heparin, NSAIDs (e.g., salicylates), radiocontrast agents (e.g., ipodate)</td>
</tr>
<tr>
<td>Increased hepatic metabolism</td>
<td>Carbamazepine, mitotane, phenobarbital, phenytoin, rifampin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Decreased 5’-deiodinase activity (T₄ converts to T₃)</td>
<td>Amiodarone, glucocorticoids, propanolol, propylthiouracil, radiocontrast agents (e.g., ipodate), tricyclic antidepressants</td>
<td>Amiodarone, glucocorticoids, propanolol, radiocontrast agents (e.g., ipodate), tricyclic antidepressants</td>
</tr>
</tbody>
</table>
Although sulfonamides have demonstrated a marked goitrogenic effect on rodents and neonatal pigs, their influence on fetal dogs appears inconsequential. In a study of puppies from four dogs treated with trimethoprim–sulfadiazine (30 mg/kg PO q24h) during gestation, no effect on serum concentration of T₄ or T₃ or aberrancy in thyroid histology was noted nor was there an increase in stillbirths, weak puppies, or gestation period between treatment and control groups.¹⁹

**NSAIDs**

NSAIDs result in altered thyroid function tests in rats and humans, mainly via altered binding of thyroid hormones to plasma transport proteins. Because circulating thyroid hormones are highly protein bound, various NSAIDs can displace thyroid hormones from their serum protein-binding sites, resulting in a transient increase in serum fT₄ concentration. The elevated fT₄ concentration serves as negative feedback to the hypothalamus and pituitary, ultimately resulting in decreased serum T₄ concentrations despite normal fT₄ concentrations. These animals remain euthyroid, but the alteration of thyroid function tests may lead to a misdiagnosis of hypothyroidism if only T₄ is measured. Deiodination of thyroid hormones may also be decreased slightly.

In humans, salicylates inhibit the binding of T₄ to all plasma transport proteins, resulting in a decrease in T₄ and a transient increase in fT₄.²⁰ With sustained use, these agents cause a 20% to 40% decrease in T₄ concentrations but do not alter fT₄.²¹,²² Other studies of various NSAIDs (e.g., oxaprozin, ketoprofen, etodolac) given at therapeutic doses for more than 3 weeks demonstrated no change in T₄ concentrations, but ketoprofen and nabumetone caused a decrease in serum T₃ concentration. A similar effect has been demonstrated with diclofenac and naproxen as well.²²,²³ Impaired 5'-deiodination may be responsible for the decrease in serum T₃ that sometimes occurs during treatment with NSAIDs.

Data on NSAIDs are limited in dogs, but carprofen (2.2 to 3.3 mg/kg PO q12h) given for 5 weeks resulted in a small but statistically significant decrease in T₄ (20.8 to 17.0 nmol/L) and TSH (0.16 to 0.12 ng/ml) concentrations without altering serum fT₄.²⁴ In another study, 19 healthy dogs were given etodolac (15 mg/kg PO q12h) for 4 weeks; and no significant change in T₄, fT₄, T₃, or TSH was noted.²⁵ In vitro studies have demonstrated that phenylbutazone had no significant effect on T₄ binding to canine serum proteins, but flunixin did decrease T₄ binding, resulting in an increase in the free fraction of T₄.²⁶
Although some NSAIDs lower serum T₄ concentrations in both humans and dogs, the magnitude of the decrease is usually minor and, to our knowledge, no cases of NSAID-induced hypothyroidism have been reported. Because the primary effect of NSAIDs is on plasma transport, serum fT₄ and TSH concentrations would be unlikely to substantially change during long-term treatment. If it is necessary to evaluate thyroid function in dogs receiving NSAIDs, it seems prudent to recommend cessation of treatment for 7 to 10 days before testing and to include measurement of serum fT₄ (by equilibrium dialysis and TSH) because T₄ concentrations may not accurately reflect thyroid function.

**GLUCOCORTICOIDs**

In various studies conducted in humans, it has been shown that not only do endogenous or exogenous glucocorticoids influence peripheral metabolism of thyroid hormones, they also directly inhibit TSH secretion. One of the principal actions of glucocorticoids is inhibition of 5'-deiodinase, resulting in decreased conversion of T₂ to T₃ and decreased rT₃ metabolism. Glucocorticoids decrease the binding of T₄ to thyroxine-binding globulin and increase binding to thyroxine-binding prealbumin; they may also alter thyroid hormone transfer from plasma into various tissues. In addition, TSH secretion in humans is impaired by glucocorticoid administration. As with many drug-induced alterations, their effects in dogs depend on multiple variables, including dose, duration of treatment, route of administration, and preparation used.

Treatment of dogs with prednisolone (1.1 mg/kg PO q12h) resulted in a decrease in serum T₄ concentration by 33% and serum T₃ concentration by 40% the first day after treatment was initiated. This decrease was sustained or became greater throughout the 3-week treatment period. In addition, serum T₄ and T₃ responses to TSH and TRH administration were reduced. In a study of similar duration using a higher dose of prednisone (1.2 to 2.0 mg/kg PO q12h), serum T₄ concentration was similar to the pretreatment level 2 days after starting treatment but was significantly decreased to less than 50% of control dogs at weeks 1 and 3 of treatment. Serum fT₄ concentration measured by equilibrium dialysis was significantly decreased at week 3 of prednisone treatment while serum TSH concentration was unchanged. After cessation of prednisone treatment, serum T₄ and fT₄ returned to baseline concentrations within 1 week. Dogs that were administered a single dose of dexamethasone (0.5 to 0.7 mg/kg PO) had a significant decrease in serum T₄ concentration 24 hours after treatment that resolved 24 hours later. Although serum T₄ was not altered by dexamethasone, serum rT₃ concentration was markedly increased for more than 48 hours. When administered at 2.2 mg/kg IM every other day, prednisone significantly decreased serum T₄ concentration 24 hours after the first dose; although subsequent measurements were variable, decreased serum T₃ concentrations were present 9 and 11 days after treatment was initiated. Serum T₃ concentration was consistently decreased to 50% or less of the pretreatment value for the duration of the 11-day treatment period. A study using an identical dose and route of prednisone administration for 21 days' duration showed a marked decrease in serum T₄ and T₃ concentrations, in addition to suppressed T₄ response to TRH and T₃ response to TSH.

Using a lower dose of prednisone (0.55 mg/kg PO q12h) for 35 days, Moore and colleagues showed a decrease in serum T₃ concentration after 2 and 4 weeks but failed to demonstrate any significant alteration in T₄, fT₄, free T₃, or rT₃ concentrations. Serum T₃ concentrations returned to normal within 2 weeks of discontinuing prednisone treatment. Using an identical dose of prednisone, Kaptein and others evaluated the effects of prednisone on T₃ and T₄ kinetics in thyroidectomized levothyroxine-replaced dogs. Prednisone treatment lowered the percent free fraction of T₄ by 30%, T₃ by 40%, and free T₃ by 49%; there was no change in total T₄ or fT₄ concentrations or percent free fraction of T₃. The investigators hypothesized that the changes noted were due to several peripheral effects of chronic prednisone use, including increased T₃ binding to serum carrier proteins, decreased fractional transfer rates of T₃ from the extravascular space into plasma, redistribution of thyroid hormones from the plasma to the muscle and skin, and decreased conversion of T₄ to T₃, resulting in lower serum T₃ levels. These findings do not necessarily correlate with changes induced by higher doses of glucocorticoids in dogs with an intact HPT axis. Although all thyroid hormones are influenced by glucocorticoids, T₃ appears to be affected earlier and more extensively. Because T₄ is primarily an intracellular hormone and approximately 50% of circulating T₄ is derived from deiodination of T₂, serum T₃ concentration is a poor measure of thyroid function in most cases.

Prednisone administration does not appear to have substantial effects on serum TSH concentration in either euthyroid or hypothyroid dogs. However, euthyroid dogs treated with prednisone had decreases in T₃ and fT₄ levels that should have resulted in an increase in serum TSH concentration because of reduced negative feedback of these hormones on pituitary thyrotropes. Failure of TSH to increase may indicate some impairment of pituitary function.
Conclusions based on available data are that glucocorticoids administered orally at an immunosuppressive dose (1 to 2 mg/kg q12h) result in rapid, consistent, and substantial decreases in $T_4$, $fT_4$, and $T_3$ concentrations. When a moderate immunosuppressive dose of prednisone is used for 3 weeks or less, serum $T_4$ and $fT_4$ concentrations should return to normal within 1 week of stopping prednisone treatment. Longer treatment may result in a longer duration of suppressed thyroid function. Because of the decrease in both $fT_4$ and $T_4$, some dogs treated with glucocorticoids may be hypothyroid. In these cases, we do not recommend thyroid hormone supplementation because animals will return to euthyroid status once treatment is discontinued.

ANTICONVULSANTS
Phenobarbital

Studies in humans and rats have demonstrated that phenobarbital alters thyroid function tests by enhancing hepatic $T_4$ metabolism secondary to hepatic microsomal enzyme induction. This increases peripheral elimination of $T_4$ via increased hepatic deiodination of thyroid hormones that results in decreased concentrations of circulating $T_4$. Enhanced biliary and fecal excretion of thyroid hormones after glucuronidation probably contributes considerably to decreases in serum thyroid hormone concentrations. This may be particularly important in dogs because about 50% of $T_4$ and 30% of $T_3$ are excreted in the feces.

Long-term administration of phenobarbital to dogs has consistently caused decreases in serum concentrations of $T_4$ and $fT_4$ and elevation of TSH. Serum $T_4$ and $fT_4$ concentrations may be below the normal range and serum TSH above the reference range in some dogs treated with phenobarbital. The decreases in $T_4$ and $fT_4$ may occur as early as 3 to 5 weeks after initiating treatment. Serum TSH concentration increased only after treatment for 6 months or more. An in vitro study of the effects of phenobarbital and phenytoin on $T_4$ binding in canine serum showed that phenobarbital did not alter $T_4$ binding whereas phenytoin decreased binding of $T_4$ to plasma transport proteins.

Given the current data, phenobarbital can markedly alter canine thyroid function, resulting in decreased serum $T_4$ and $fT_4$ concentrations, which may be accompanied by slightly elevated TSH concentrations. These findings are consistent with hypothyroidism. Because clinical signs of hypothyroidism and side effects of phenobarbital administration (e.g., lethargy, weight gain) can be similar, it may be difficult to accu-
rately assess thyroid function in dogs given phenobarbital. As a result, thyroid function tests should be cautiously interpreted in dogs receiving anticonvulsant therapy with phenobarbital. Thyroid function normalized by 4 weeks after withdrawal of phenobarbital, indicating that this may be an appropriate time for retesting thyroid function. However, cessation of phenobarbital administration might carry risks that make this recommendation inappropriate. Therefore, if clinical signs and thyroid function tests are compatible with hypothyroidism, a trial of levothyroxine therapy may be warranted.

**Potassium Bromide**

As an alternative or adjunct therapy to phenobarbital, potassium bromide (KBr) is used extensively to treat canine epilepsy. This medication may affect thyroid function because bromide is a halide similar to iodide. KBr administration leads to goiter in rats. A small study of epileptic dogs administered KBr for a median of 14.5 months failed to find altered thyroid function test results. These findings were confirmed in a recent study of healthy dogs receiving KBr over 6 months, in which thyroid function (T3, TSH, and fT4 concentrations) remained unchanged. Therefore, it appears that administration of KBr does not significantly affect thyroid function in dogs when used at appropriate doses.

**PROPRANOLOL**

Altered thyroid hormone metabolism in humans has occurred with the use of the β-adrenergic blocker propranolol. Small decreases in serum T3 are present because of decreased activity of 5′-deiodinase. In the only reported study in healthy beagles given propranolol (20 mg PO q8h for 2 weeks, increased to 40 mg PO q8h for an additional 2 weeks), thyroid hormone concentrations and TSH stimulation test results were not altered. Therefore, administration of propranolol in euthyroid dogs is unlikely to alter thyroid function tests during short-term treatment, but the effects of prolonged administration are unknown.

**TRICYCLIC ANTIDEPRESSANTS**

Administration of tricyclic antidepressants in humans and rats has been extensively documented to alter thyroid function, either through binding of iodine (rendering it unavailable), inhibiting thyroid peroxidase (decreasing thyroid hormone production), stimulating deiodinase activity (increasing T4 degradation), or directly interfering with the HPT axis (via manipulation of the noradrenergic and serotonergic systems that interact with the hypothalamus, directly increasing or decreasing TRH release depending on the conditions under which studies were conducted). The use of tricyclic antidepressants in companion animal medicine is on the rise, especially with the recent introduction of clomipramine for the treatment of canine separation anxiety. A recent study of clomipramine administered long term to euthyroid dogs indicated a statistically significant decrease of about 30% in serum T3, fT4, and rT3 concentrations. A decrease of this magnitude may be clinically important because animals with low-normal thyroid hormone levels may become clinically hypothyroid. Furthermore, the effect of clomipramine on thyroid function tests may result in a misdiagnosis of hypothyroidism if a dog is tested while taking this medication. It is not known how long the drug must be discontinued prior to obtaining valid test results.

**FUROSEMIDE**

In humans, administration of high doses of furosemide induces a decrease in serum T3 concentration and an increase in serum fT4 concentration, consistent with impaired plasma protein binding of T4. An in vitro study of canine serum demonstrated that furosemide markedly impairs binding of T3 to plasma proteins. It is surmised that this would result in a similar increase in fT4 concentration and a decrease in T4 concentration, as seen in the human literature, but additional studies evaluating thyroid function tests in dogs have not been completed. Until further studies are completed, it is prudent to cautiously interpret thyroid hormone concentrations in animals that have been on long-term maintenance therapy.

**STANOZOLOL**

Androgens consistently decrease serum concentrations of T3 and T4 in humans by decreasing the binding capacity or circulating concentrations of T4-binding globulin, while effects on fT3 and TSH are variable. The specific effects vary depending on the composition of the anabolic steroid and the dose administered. In the only study in dogs known to us, the anabolic steroid stanozolol (2 mg PO q12h) was administered to six healthy dogs for 3 weeks, and no effect on serum T3, T4, or rT3 concentrations was noted. Therefore, it can be assumed that when used for 3 weeks or less, this medication should have a minimal effect on thyroid function tests.

**AMIODARONE**

Amiodarone is a benzofuranic derivative that structurally resembles T3 and contains 37% iodine by weight. It is a class III antiarrhythmic drug that has been used in dogs. In humans, amiodarone may cause altered thyroid function tests and sometimes hyperthyroidism or
hypothyroidism. Amiodarone affects thyroid function by inhibiting 5'-deiodinase activity, inhibiting T₄ entry into tissue, competing with binding of T₃ to thyroid hormone receptors, decreasing thyroid cell response to TSH, and reducing TSH synthesis and secretion in the pituitary. Hypothyroidism may occur secondary to exacerbation of preexisting thyroiditis or because of the inability of the thyroid gland to escape from the suppressive effects of excess iodine on thyroid hormone synthesis and secretion (Wolff-Chaikoff effect). The thyrotoxicosis is thought to be due to a direct cytotoxic effect of amiodarone or the result of iodine-induced overproduction of thyroid hormones secondary to the large amount of iodine released from the medication.

Amiodarone administration (22 to 36 mg/kg/day for 4 weeks) to normal dogs resulted in an increase in serum T₄ concentration by over 50% without an effect on serum T₃. Serum amiodarone concentrations in these dogs were 2 ½ to 3 times higher than recommended for the desired clinical effects. These findings are consistent with decreased activity of 5'-deiodinase. Another study evaluating the in vitro effects of amiodarone on canine thyroid gland secretion demonstrated inhibition of TSH-induced thyroid hormone secretion. The effects of therapeutic doses of amiodarone on thyroid function in dogs remain to be determined. Until then, it is advisable to periodically monitor thyroid function tests in dogs given amiodarone because hyper- and hypothyroidism have adverse cardiovascular effects.

Cytokines

Treatment of neoplasms and some infectious diseases with immunotherapy is becoming more widely used in human and veterinary medicine. Cytokines and interferons are molecules that modulate the immune response. Two of the most common agents used for immunotherapy are interleukin-2 (IL-2) and interferon-α (although other cytokines and interferons have also been used). These agents can induce thyroid dysfunction, either by causing progression of preexisting autoimmune thyroid disease or through induction of changes seen with euthyroid sick syndrome. The only study evaluating the effects of immunotherapy on thyroid function tests in dogs evaluated the response to high-dose IL-2 administration. A decrease in serum concentrations of T₄ and T₃ to less than 50% of baseline was noted during the infusion. No dog had antithyroglobulin antibodies after IL-2 administration, suggesting that short-term administration of IL-2 does not induce thyroid autoimmunity in dogs. It is recommended that thyroid function not be evaluated in dogs...
undergoing immunotherapy and that testing be delayed until treatment is completed.

**RADIOCONTRAST AGENTS**

Oral cholecystographic contrast agents, ipodate and iopanoic acid, have been shown to affect the thyroid in numerous ways, including potent inhibition of 5’-deiodinase, resulting in a substantial decrease in serum $T_3$ concentrations in human and feline hyperthyroid patients. $^{60,61}$ Inhibition of deiodination has been demonstrated in isolated canine thyroid glands, and increases in $T_3$ concentrations and a decrease in $T_4$ concentrations by approximately 50% of baseline were noted for at least 48 hours following administration of a single dose of 6 g to normal dogs. $^{31,62}$ Ipodate also causes a displacement of $T_3$ from binding sites in hepatocytes and carrier proteins, and the excess iodine released from the medication may block thyroid secretion of $T_4$. $^{63}$ Thyroid function should not be evaluated in dogs that have recently received an oral cholecystographic contrast agent.

**HEPARIN**

Human studies have demonstrated a transient increase in $fT_3$ concentration following the administration of heparin, and in vitro studies have reported this is due to inhibition of $T_3$ binding to plasma proteins secondary to free fatty acids generated as a consequence of heparin activation of lipoprotein lipase. $^{65-67}$ Although no studies on the effects of heparin on thyroid function have been conducted in vivo in dogs, a study of the in vitro influence of heparin on $T_3$ binding to plasma proteins demonstrated an increase in binding of $T_3$. This change would be expected to increase total $T_3$ concentration and reduce $fT_3$ concentration. $^{26}$ Heparin’s effect on thyroid hormone concentrations may be important in hospitalized animals with indwelling intravenous catheters in which heparin is flushed through the catheter frequently or in any animal receiving heparin for anticoagulant therapy. Until further investigation is undertaken, thyroid function testing should be delayed until heparin therapy is discontinued.

**THYROXINE SUPPLEMENTATION**

A common situation to encounter in practice is evaluation of thyroid function in an animal that has been empirically treated with levothyroxine without appropriate testing for hypothyroidism. Administration of levothyroxine to a euthyroid dog will cause decreased TSH secretion and, therefore, decreased endogenous thyroid hormone secretion. Prolonged treatment will result in atrophy of pituitary thyrotropes and the thyroid. After 8 weeks of administration of a replacement dose of levothyroxine, thyroid function is suppressed for at least 4 weeks. $^{67}$ Current recommendations for testing thyroid function in animals being administered levothyroxine are to discontinue treatment and measure $T_4$, $fT_4$, and TSH concentrations after 8 weeks. If thyroid hormone supplementation has been administered for many months, significant thyrotrope atrophy may have occurred, and recovery of the HPT axis may take much longer than 8 weeks. Recovery from prolonged levothyroxine administration may take more than a year in humans, during which time they may become clinically hypothyroid. $^{68}$ Therefore, for dogs given levothyroxine for a year or longer, the advantages of discontinuing therapy and establishing the functional status of the thyroid must be carefully weighed against continuing levothyroxine supplementation.

Administration of some drugs can reduce absorption of orally administered levothyroxine in humans. Decreased absorption of levothyroxine has been reported in hypothyroid humans who concurrently take aluminum hydroxide, ferrous sulfate, or sucralfate. $^{69}$ It is possible that these medications may have the same effect in dogs, although specific studies are lacking. If a hypothyroid dog on levothyroxine supplementation is treated with one of these drugs, it would be prudent to administer them several hours apart to ensure proper absorption. In addition, therapeutic monitoring of serum $T_4$ and TSH concentrations is recommended to determine if adjustment of the levothyroxine dose is necessary.

**CONCLUSION**

Many different drugs affect thyroid function tests. The list of drugs known to affect thyroid function in humans is much more extensive than those evaluated in dogs (Table 1). Awareness of the medications that alter thyroid hormone concentrations or elevate serum TSH will facilitate a more accurate interpretation of test results, hopefully avoiding the erroneous diagnosis of hypothyroidism and subsequent unwarranted treatment.

As with any clinicopathologic test result, aberrant thyroid hormone concentrations should be interpreted in conjunction with a complete history and compatible physical examination findings. Results of thyroid function tests should be carefully scrutinized in patients with a history of medication usage, especially glucocorticoids, NSAIDs, phenobarbital, sulfonamides, furosemide, or clomipramine. As with any medication, doses and length of treatment are essential considerations. Finally, it is important to realize that the various mechanisms through which these drugs alter canine thyroid function have not been fully elucidated, and the effects of many other commonly used medications on canine thyroid function remain to be evaluated.
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1. The enzyme thyroid peroxidase is responsible for
   a. organification (oxidization) of iodine.
   b. binding iodine to thyroglobulin and formation of mono- and diiodotyrosine.
   c. formation of T₃ and T₄.
   d. all of the above

2. Which of the following compounds has the highest affinity for binding T₄ in the plasma?
   a. T₄-binding globulin
   b. T₄-binding prealbumin
   c. albumin
   d. none of the above

3. Which of the following drugs is likely to cause clinical signs of hypothyroidism in dogs when administered for more than 6 weeks?
   a. glucocorticoids
   b. sulfonamides
   c. phenobarbital
   d. furosemide

4. What alteration in tests of thyroid function would be expected in dogs given immunosuppressive doses of prednisone for more than 2 weeks?
   a. decreased T₃
   b. decreased T₄
   c. decreased fT₄
   d. all of the above

5. If a canine patient is given immunosuppressive doses of glucocorticoids for 2 to 4 weeks, the *minimum* time to wait before conducting thyroid testing is
   a. 1 week.
   b. 2 to 3 weeks.
   c. 4 to 6 weeks.
   d. There is no need to wait before testing.

6. In well-controlled epileptic patients on phenobarbital therapy, which of the following is a likely alteration found on thyroid testing?
   a. decreased TSH
   b. increased T₄
   c. decreased fT₄
   d. increased T₃

7. When given at the recommended dose, how does KBr affect thyroid function?
   a. increases T₃
   b. has no effect
   c. increases rT₃
   d. increases T₃, T₄, and fT₄

8. Which of the following medications, when given at recommended doses, has been shown to decrease serum T₃, fT₄, and rT₃ concentrations by approximately 30%?
   a. propranolol
   b. clomipramine
   c. furosemide
   d. stanozolol

9. Phenobarbital is thought to cause a decrease in circulating T₄ by
   a. increasing thyroid hormone metabolism.
   b. inhibiting thyroid peroxidase.
   c. stimulating secretion of TRH.
   d. preventing binding of T₄ in the serum.

10. If a canine patient is given the recommended dose of levothyroxine for 8 weeks, the *minimum* time to wait before conducting thyroid testing is ______ week(s).
   a. 1
   b. 2 to 3
   c. 4 to 6
   d. 8