Proceedings of the European Veterinary Conference
Voorjaarsdagen

Amsterdam, the Netherlands
Apr. 18 - 20, 2013

Next Meeting:

Apr. 17 – 19, 2014 - Amsterdam, the Netherlands

Reprinted in IVIS with the permission of the Conference Organizers
http://www.ivis.org
THE DIAGNOSTIC APPROACH OF HYPERCORTISOLISM IN THE DOG

Introduction

Hypercortisolism is a common condition in dogs and can be defined as the physical and biochemical changes that result from prolonged exposure to inappropriately high plasma cortisol concentrations, whatever its cause. This disorder is often called Cush- ing’s syndrome, after Harvey Cushing, the neurosurgeon who first described the human syndrome in 1932.

Cushing's syndrome is frequently iatrogenic, in most cases due to administration of glucocorticoids for the treatment of a variety of allergic, autoimmune, inflammatory or neoplastic diseases. This abstract will focus on the diagnosis of spontaneous hypercortisolism. In 80-85% of the spontaneous cases hypercortisolism is adrenocorticotropic hormone (ACTH)-dependent, usually arising from hypersecretion of ACTH by a pituitary corticotroph adenoma. The remaining 15-20% of cases of spontaneous hypercortisolism is ACTH-independent and result mainly from autonomous glucocorticoids hypersecretion by an adrenocortical tumor.

Diagnosis of hypercortisolism

The endocrine diagnosis of hypercortisolism depends on the demonstration of two principal characteristics: (1) increased production of cortisol, and (2) decreased sensitivity to glucocorticoid feedback. Measurement of a single plasma cortisol concentration has little diagnostic value because the pulsatile secretion of ACTH results in variable plasma cortisol concentrations that may at times be within the reference range. There are two ways to overcome this problem: (1) to test the integrity of the feedback system, and (2) to measure urinary corticoid excretion.

In the first approach the sensitivity of the pituitary-adrenocortical system to suppression is tested by administering a synthetic glucocorticoid in a dose that discriminates between healthy dogs and dogs with hypercortisolism. In this so-called dexamethasone screening test or low-dose dexamethasone suppression test (iv-LDDST), 0.01 mg dexamethasone per kg body weight is administered intravenously. Blood for cortisol measurement is collected before, and 4 h and 8 h after dexamethasone administration. The finding of a plasma cortisol concentration exceeding 40 nmol/l at 8 h after dexamethasone administration, in dogs with physical and biochemical changes pointing to hypercortisolism, confirms hypercortisolism. The measurements at 0 h and 4 h are not needed for the diagnosis per se but may be useful in the differential diagnosis. If the plasma cortisol concentration at either 4 h or 8 h is at least 50% lower than the 0 h value, the hypercortisolism is pituitary-dependent. The iv-LDDST can be false positive as a result of stress, for example due to chronic illness.

This iv-LDDST is increasingly replaced by the measurement of urinary corticoids. Because urine is stored and mixed in the bladder for several hours an integrated reflection of corticoid production is obtained, thereby adjusting for fluctuations in plasma concentrations. The urinary corticoids (largely cortisol) are related to the creatinine concentration in the urine, resulting in the urinary corticoid to creatinine ratio (UCCR). This test requires little time (from the veterinarian and the owner), is not invasive, and has a high diagnostic accuracy. To avoid the influence of stress, the urine for the UCCR determination has to be collected at home, at least one day after the visit to the veterinary clinic. Nonadrenal disease may also result in endogenous stress and elevated cortisol secretion and therefore high UCRs in dogs that do not have a high degree of clinical suspicion should be interpreted with care. For the determination of the UCCR only labs should be used that use a validated assay for measurement of urinary corticoids and that have determined reference values.

Another popular test to screen for hypercortisolism is the ACTH stimulation test. The main indication for the ACTH stimulation test is to test the adrenocortical reserve capacity, i.e., to diagnose primary or secondary adrenocortical insufficiency. Thus, the ACTH stimulation test can be used very well to diagnose iatrogenic hypercorticism. In cases of spontaneous hypercortisolism, ACTH stimulation may result in an exaggerated adrenal response, i.e., a higher plasma cortisol concentration than in healthy dogs. About 85% of dogs with pituitary-dependent hypercortisolism have exaggerated cortisol responses to ACTH, while only about 55% of dogs with hypercortisolism due to adrenocortical tumor have such a result. The main advantages of the ACTH stimulation
test are its simplicity and the short duration of the test. However, the diagnostic accuracy for hypercortisolism of this test is less than that of the UCCR and the LDDST. Therefore, this test is no longer recommended in the diagnostic approach of dogs with hypercortisolism.

When hypercortisolism has been confirmed it is necessary to distinguish between the different forms of the disease. The impaired sensitivity to glucocorticoid feedback in most cases of pituitary-dependent hypercortisolism can be demonstrated by performing a high-dose dexamethasone suppression test. A decrease of more than 50% from baseline values confirms pituitary dependency. Further differentiation requires measurements of plasma ACTH concentrations. In animals with pituitary-dependent hypercortisolism, plasma ACTH concentrations are not completely suppressed despite high plasma cortisol concentrations. The preferred procedures for imaging are MRI and CT. Ultrasonography is less expensive, requires less time, and usually no anesthesia, and so it is often used first even though it is more difficult to perform and to interpret than CT or MRI. Ultrasonography provides a good estimate of the size and expansion of an adrenal tumor. In case of an adrenal tumor, the possibility of distant metastases, especially in liver and lungs should be considered.

Reference
TREATMENT OF CANINE HYPERCORTISOLISM

Pituitary-dependent hypercortisolism

Hypophysectomy
There is increasing evidence that the primary lesion is at pituitary level and not the result of increased hypothalamic stimulation. Consequently hypophysectomy is being revisited. Visualization techniques have become available that enable presurgical insight into the size and expansion of the lesion. This in combination with improved surgical and anesthetic techniques now permits removal of rather large tumors. Pituitary surgery requires a team approach and the neurosurgeon performing hypophysectomies must master a learning curve. The long-term survival of hypophysectomy compares favorably with that of treatment with o,p'-'DDD.

Radiation therapy
There is also the option of radiation therapy for pituitary adenomas. This may lead to some decrease in the tumor mass and peritumoral edema, but concurrent adrenocortical suppression treatment is almost always needed.

Adrenalectomy
Other approaches are directed at the elimination of the glucocorticoid excess, either by bilateral adrenalectomy or by chemotherapy. With total adrenalectomy in dogs the cure is 100% and the prognosis with glucocorticoid and mineralocorticoid replacement is good, unless the expansion of the pituitary lesion gives rise to neurological signs.

Inhibition of steroidogenesis
Another therapeutic option is the inhibition of adrenocortical steroidogenesis. This can be achieved by ketoconazole, a synthetic imidazole analogue used as a broad-spectrum antifungal agent. In addition to its antifungal activity, ketoconazole has been demonstrated to interfere with gonadal and adrenal steroid synthesis through inhibition of cytochrome P-450-dependent enzymes. The major limitations in using ketoconazole in dogs are (1) the need for continuing twice daily administration, (2) the expense, and (3) the failure of some dogs to respond. In addition there may be hepatotoxic effects.

During the last years trilostane has been used increasingly for the treatment of canine hypercortisolism. Trilostane is an inhibitor of 3β-hydroxysteroid dehydrogenase, which blocks the conversion of pregnenolone to progesterone. The signs and symptoms usually begin to abate within a few days, at least when the optimal dosage is given. Following an initial dose of about 2 mg/kg body weight per 24 h the dose rates are adjusted according to the physical changes and laboratory tests (including an ACTH-stimulation test). There appears to be a wide variation in the effectiveness between individual dogs. In some cases dose rates up to 10 mg/kg or higher per 24 h may be needed, but the median optimal dosage is about 3 mg/kg per 24 h. Trilostane administration decreases the plasma cortisol concentrations only for a few hours. However, even with once daily administrations this seems to be sufficient to ameliorate the signs and symptoms, although treatment will not always result in hematological and biochemical improvements. It is important to know when the drug was given, when an ACTH-stimulation test is considered to assess the effectiveness of the treatment. As this enzyme inhibitor not only blocks the glucocorticoid pathway but also the mineralocorticoid pathway, there is the risk of inducing hypoadrenocorticism.

Treatment with trilostane leads to distinct adrenocortical enlargement, attributable to increased stimulation by pituitary ACTH. After treatment for 1 year or longer the adrenal glands may assume an irregular shape with nodular hyperplasia. In addition, trilostane may result in bleeding and necrosis in the zona fasciculata, resulting in hypocortisolism. Because trilostane (similar to o,p'-'DDD) does not influence the causative lesion at pituitary level, in some cases ongoing growth of the pituitary tumor may ultimately prohibit long term survival.

Chemotherapy
Complete destruction of the adrenal cortices can be achieved by chemotherapy with o,p'-'DDD (Lysodren*) in a dosage of 50-100 mg o,p'-'DDD/kg per day given for 25 days. This daily dose should be divided into three or four portions and administered with food. On the third day, supplementation begins (cortisone acetate, 2 mg/kg per day, fludrocortisone, 0.0125 mg/kg per day, and sodium chloride, 0.1 g/kg per day); all doses are divided into at least two administrations. After 25-30 days, a follow-up examination is made. The cortisone dose is reduced to 0.5-1.0 mg/kg per day. Fludrocortisone and/or
Salt are adjusted according to the results of measurements of Na and K in plasma. Despite this drastic treatment schedule, recurrences do occur in about 30% of cases within one year. The owner may call because the animal's appetite and water intake have increased. Omitting the cortisone substitution may ameliorate the signs temporarily, but the possible recurrence should be investigated by asking the owner to send urine specimens for measurements of corticoid/creatinine ratios. Two morning urine samples are collected at an interval of 4 to 5 days, each time omitting the cortisone and fludrocortisone administration on the preceding evening. Ratios exceeding the upper limit of the reference range indicate glucocorticoid excess, and o,p'-DDD therapy is then started for another 25 days, followed by once weekly administration of o,p'-DDD for 8 weeks. Substitution therapy and follow-up examinations are carried out as in the first course. In case of a second recurrence, this procedure is repeated and the weekly o,p'-DDD dose is continued lifelong.

**Hypercortisolism due to adrenocortical tumors.**

When the preoperative investigations have revealed that it is likely that there is a resectable unilateral tumor without metastases, it should be treated by surgery, because the successful removal of the tumor will result in complete recovery without the need for continuing medication. The perioperative period is critical. Once survived this period, in most cases there is long-term resolution of signs and symptoms. Because of the atrophy of the contralateral adrenal cortex, due to the longstanding glucocorticoid excess, glucocorticoid substitution is needed initially. At the time of anesthesia, when intravenous fluid administration is started, 5 mg hydrocortisone or 1 mg prednisone per kg body weight is added to the first bottle and this amount is administered over a period of 6 h. Subsequently 0.5 mg hydrocortisone/kg is administered at 6 h intervals until oral medication is possible. This will consist of 1 mg cortisone/kg body weight twice daily, which is gradually decreased and then stopped 6-8 weeks after surgery.

Dogs with irresectable tumor or recurrence of disease after adrenalectomy can often be treated successfully with o,p'-DDD, thereby initially employing the same schedule as for pituitary-dependent hypercortisolism (see above). After 25 days of daily administrations of 50-75 mg o,p'-DDD/kg, this chemotherapy is continued for at least three months by once weekly administrations of the same daily dose. This approach often leads to complete and permanent cure of the hypercortisolism, and ultrasonographic examinations may reveal that the size of the tumor has decreased considerably. Even lung metastases may disappear, although it may also happen that this tumor dissemination cannot be influenced.

Although surgical removal of the tumor is the most attractive option, there is also the possibility to inhibit steroidogenesis in these tumors with trilostane.

**Reference**

DIFFICULT CASES OF CANINE HYPERADRENOCORTICISM

Introduction
A hyperfunction of the adrenal cortex, i.e., hyperadrenocorticism, may result in hypercortisolism, hyperaldosteronism and/or hyperandrogenism. Spontaneous hypercortisolism is a common disorder in dogs and can be defined as the physical and biochemical changes that result from prolonged exposure to inappropriately high plasma cortisol concentrations. In 80-85% of the spontaneous cases hypercortisolism is adrenocorticotropin hormone (ACTH)-dependent, usually arising from hypersecretion of ACTH by a pituitary corticotroph adenoma and rarely due to ectopic ACTH-secretion. The remaining 15-20% of cases of spontaneous hypercortisolism is ACTH-independent and result from autonomous hypersecretion of glucocorticoids by an adrenocortical adenoma or adrenal carcinoma. In addition to an adrenocortical tumor, ACTH-independent hypercortisolism can be caused by bilateral (macro)nodular adrenocortical hyperplasia as a result of aberrant adrenal expression of either ectopic or overactive eutopic hormone receptors.

Hypercortisolism due to ectopic ACTH secretion
Ectopic ACTH hypersecretion has been documented in an 8-year-old German shepherd dog. The UCCRs and plasma ACTH concentrations were very high and not suppressible with dexamethasone. These findings were initially interpreted as being consistent with pituitary-dependent hypercortisolism (PDH). However, histological examination of the tissue removed by transsphenoidal hypophysectomy did not confirm the presence of an adenoma. Within two weeks after hypophysectomy the clinical manifestations were exacerbated and both the UCCR and plasma ACTH concentration were further increased. CT of the abdomen revealed a tumor in the region of the pancreas. Laparotomy revealed a 5-mm nodule in the pancreas, a 3-cm metastasis in an adjacent lymph node, and metastases in the liver. Partial pancreatectomy and excision of the lymph node were performed, and a neuroendocrine tumor with metastasis in the lymph node was diagnosed by histopathology. Based on this report, ectopic ACTH secretion should be considered in cases of severe hypercortisolism in which plasma ACTH concentrations are very high and are not suppressible with high doses of dexamethasone, and in which diagnostic imaging does not reveal a pituitary tumor. In patients with PDH intravenous administration of 1 μg corticotropin-releasing hormone (CRH) per kg body weight results in a significant increase in plasma concentrations of ACTH and cortisol, but in patients with ectopic ACTH secretion CRH does not increase these plasma hormone concentrations. The neuroendocrine tumor causing the ectopic ACTH syndrome may be detected by a whole-body scan, but in human patients with ectopic ACTH syndrome the tumors are frequently small and often not found.

Hypercortisolism due to ectopic or hyperactive eutopic adrenocortical receptors
In addition to autonomous cortisol secretion by an adrenocortical tumor (AT), ACTH-independent hypercortisolism can also be caused by aberrant adrenal expression of either ectopic or overexpressed eutopic hormone receptors. Most of these hormone receptors belong to the superfamily of G protein-coupled receptors. In humans, various adrenocortical membrane-bound receptors functionally coupled to steroidogenesis have been reported, including glucose-dependent insulinotropic polypeptide (GIP), catecholamine, vasopressin, serotonin, and luteinizing hormone receptors.

In a recently published case report of a dog with food-dependent hypercortisolism, the ACTH-independent hypercortisolism was most likely due to aberrant adrenocortical expression of GIP receptors. The hormone GIP is secreted in the gastrointestinal tract in response to a meal and normally serves to enhance post-prandial insulin secretion. In human patients with aberrant adrenocortical expression of GIP receptors a meal not only results in augmented insulin secretion but also in increased steroidogenesis. The dog described in the case report had clinical manifestations of hypercortisolism and slightly elevated UCCRs. Basal and CRH-stimulated plasma ACTH concentrations were low, but diagnostic imaging did not reveal an adrenocortical tumor. Ingestion of a meal resulted in significant increases in plasma cortisol concentration and UCCR. Consistent with the diagnostic criteria for food-dependent hypercortisolism in humans, intravenous administration of 3 μg octreotide per kg body weight completely prevented the meal-induced hypercortisolemia. The dog had a good clinical response to medical treatment with trilostane, administered shortly before the main meal.

Thus, a distinct increase in UCCR and plasma cortisol concentration after ingestion of a
meal, low or undetectable plasma ACTH concentrations, and prevention of a meal-induced rise in plasma cortisol concentration by octreotide administration strongly suggest food-dependent hypercortisolism.

**Hyperadrenocorticism due to hypersecretion of mineralocorticoids**

Excessive activation of mineralocorticoid receptors can be the result of hypersecretion of aldosterone by an adrenocortical tumor. In addition, adrenocortical tumors secreting the mineralocorticoid deoxycorticosterone (DOC) have been reported in dogs. There have been two case reports of primary hyperaldosteronism in dogs, one with a small aldosteronoma and the other with a large adrenocortical carcinoma and hepatic metastases. In addition, cases of primary hyperaldosteronism have been mentioned in text books.

Mineralocorticoid excess causes two abnormalities: (1) increased sodium retention, and (2) increased potassium excretion. The initial sodium retention is followed by natriuresis, so sodium balance is reestablished and edema does not develop. Nevertheless, mineralocorticoid excess tends to be associated with extracellular fluid expansion, arterial hypertension, and increased cardiac output. In canine hyperaldosteronism the release of vasopressin following an osmotic stimulus is delayed, and there is resistance to the action of vasopressin, similar to that in hypercortisolism, explaining the polyuria in dogs with primary hyperaldosteronism.

In primary mineralocorticoid excess, the plasma concentration of aldosterone (or DOC) is characteristically high and plasma renin activity (PRA) is immeasurably low.

**References**

THE DIAGNOSTIC APPROACH TO POLYURIA IN THE DOG

Introduction
Urine osmolality (Uosm: 161 - 2830) and urine specific gravity (Usg: 1.006 - >1.050) vary widely among healthy pet dogs. In some individual dogs Uosm fluctuates considerably during the day and Uosms close to plasma osmolality (Posm) may be reached. In some pet dogs the low Uosms are associated with sufficiently high Usms at other times of the day so that the owners do not perceive their dog to be polydipsic or polyuric.

However, in other dogs the situation is more pronounced and the animals are presented to the veterinarian because of polyuria and polydipsia. Some of these animals may thus be recognised as having primary polydipsia.

Differential diagnosis
Apart from central diabetes insipidus there are in principal only two basic disorders which can account for increased water diuresis. These disorders are primary polydipsia and nephrogenic diabetes insipidus. Primary polydipsia is said to occur in hyperactive young dogs that are left alone during the day for many hours or have gone through significant changes in their environment. It has been observed that placing the animal in a completely different environment may stop the problem. The finding of the above mentioned spontaneous fluctuation of Uosm may be regarded as diagnostic of primary polydipsia. However, these irregular patterns of water intake may also be associated with abnormalities in vasopressin release. There are a few individual case reports of congenital nephrogenic diabetes insipidus, the condition in which the kidney tubules are insensitive/less sensitive to the action of antidiuretic hormone.

In addition to these two basic and infrequently encountered differential diagnoses, a wide variety of conditions causes polyuria. In the young animal this may be congenital kidney disease, whereas at all ages acquired kidney disease may lead to polyuria. Especially in the middle-aged and elderly animals (endocrine) conditions such as hyperadrenocorticism, hyperthyroidism, pyometra, progestin-induced (luteal phase) growth-hormone excess, hyperparathyroidism and hypercalcemia of malignancy have to be considered. In several of these conditions impaired release of vasopressin and/or interference with its action may play a role in the polyuria.

Hyperadrenocorticism (i.e., hypercortisolism or hyperaldosteronism) may induce impairment of the osmoregulation of vasopressin secretion. In addition, it may cause resistance to the effects of vasopressin at the level of the kidney.

Hypersomatotropism or acromegaly is a syndrome of tissue overgrowth and insulin resistance due to excessive growth hormone (GH) production. In the dog, excessive GH production can be induced either by endogenous progesterone or by exogenous progestagens used for estrus prevention. Frequently the dogs are presented with polyuria. The polyuria is usually without glucosuria, but manifest diabetes mellitus can develop due to insulin resistance.

Pyometra is a complication of cystic endometrial hyperplasia (CEH), which develops during the luteal phase of the estrous cycle or is due to exogenous progestagens used for estrus prevention. Loss of renal medullary hypertonicity, and as a consequence decreased concentrating ability, has been described as a cause of the polyuria in dogs with pyometra. The polyuria may also be the result of decreased sensitivity of the renal V2 receptors.

In virtually all dogs PU/PD is a prominent symptom of hyperthyroidism. Primary polydipsia plays an important role in the pathogenesis of PU/PD in hyperthyroidism.

Hypercalcemia may be caused by primary hyperparathyroidism or a malignancy. The latter, i.e., cancer associated hypercalcemia, is a paraneoplastic syndrome that results from the release of humoral factors (among which PTHrP) that induce hypercalcemia. This humoral hypercalcemia of malignancy frequently occurs in dogs with apocrine adenocarcinomas of the anal sac or with malignant lymphoma. The impaired urinary concentrating ability may be due to increased renal medullary blood flow, decreased solute transport out of the loop of Henle, and/or interference with the action of vasopressin at the renal level.
The PU/PD in hepatic disease is usually associated with hepato-encephalopathy. The abnormal hepatic metabolism of amino acids may give rise to “false” neurotransmitters, which may lead to elevated ACTH secretion and consequently hypercortisolism.

Pyelonephritis may destroy the hypertonic renal medulla, resulting in dilute urine. Examination of urine sediment (after cystocentesis) may reveal white blood cells and bacteria. Radiographic contrast studies and/or ultrasonographic examination of the kidneys may be helpful in the diagnosis of pyelonephritis.

**Diagnosis**

When history, physical examination and laboratory examinations do not lead to a diagnosis that might explain the polyuria, the next step can be a request to the owner to collect frequent urine samples (every 2 hours (and every 4 h during the night)) for a period of 24 h. In order to test for possible vasopressin resistance, this procedure may be repeated at the fourth day of administration of a vasopressin analogue (DDAVP, see below). When the Uosm pattern is not conclusive, a water deprivation test is most commonly used for differentiating the causes of polyuria. The test is difficult to perform correctly and unpleasant for the animal. In addition, it relies heavily on the emptying of the bladder, and is indirect because changes in urinary concentration are used as an index of vasopressin release.

In both nephrogenic diabetes insipidus and central diabetes insipidus Uosm will remain low during water deprivation. In complete diabetes insipidus Uosm will rise by 50% or more following administration of vasopressin, whereas in the partial forms of central diabetes insipidus the rise will be > 15%, and in nephrogenic diabetes insipidus there will be very little or no rise in Uosm. Because of the indirect character of the test, the results may not always be conclusive.

**Treatment**

The vasopressin analogue desmopressin (Minrin®) provides antidiuretic activity for about 8 hours. One drop placed twice daily in the conjunctival sac sufficiently controls the polyuria in most dogs with central diabetes insipidus. With the administration of three drops a day the urine production usually returns to normal, but some owners (in part for financial reasons) prefer to apply the drug only twice daily. The analogue can also be effective when administered as tablet; two or three times per day ½ tablet of 0.1 or 0.2 mg, depending on the size of the animal and the effect.

**Reference**

FELINE HYPERTHYROIDISM

Introduction
Feline hyperthyroidism is a relatively common disease of middle-aged and elderly cats, with a mean age of 12 to 13 years. There is no breed or sex predilection. The thyroid hormone excess is produced by thyroid adenomatous hyperplasia or adenoma, involving one or, more often, both thyroid lobes. Thyroid carcinoma, which is the main cause of hyperthyroidism in dogs, accounts for only about 5% of cases.

Clinical manifestations
The adenomatous glands tend not to become very large, so rarely is veterinary help sought because of a mass detected by the owner. Thus it is the signs and symptoms due to effects of thyroid hormone excess on organ systems that lead to veterinary examination. The classic presentation of a hyperthyroid cat is that of a skinny, restless, elderly cat with an increased appetite and polyuria. Many organ systems can be affected. Weight loss—often together with increased appetite—may be sufficient reason to suspect hyperthyroidism. In about 10% of cases the clinical picture may be quite different. In these cats weight loss remains an important feature, but there is lethargy and anorexia rather than hyperactivity and increased appetite.

The multisystemic effects of thyroid hormone excess not only lead to a variety of physical changes but may also give rise to several biochemical abnormalities. Most of these are reversed with treatment, including elevated plasma concentrations of liver enzymes. The hemodynamic alterations of hyperthyroidism are responsible for marked increases in the glomerular filtration rate. Of concern has been the increase in the plasma creatinine concentration after treatment of hyperthyroidism, although it is often still within the reference range. Although considered to be the unmasking of preexisting chronic kidney disease, it seems to have little clinical significance. The survival of treated hyperthyroid cats does not seem to be affected by post-treatment azotemia.

Diagnosis
When hyperthyroidism is suspected, the first step should be a careful palpation of the neck area by gently sliding the thumb and index finger along the sides of the trachea. Enlargement of one or both lobes can be found by an experienced examiner in up to 90% of cats with hyperthyroidism.

The final diagnosis ought to rest on a direct measurement of thyroid function. In about 90% of cats presented with the syndrome of hyperthyroidism, the T4 concentration in plasma exceeds the upper limit of the reference range. Plasma T4 concentration fluctuates over time and in cats with mild hyperthyroidism, T4 values may be in the high-normal range. In addition, concomitant nonthyroidal disease may lower the value below the reference range. When plasma T4 concentration falls within the reference range and the animal is still suspected of hyperthyroidism, the measurement of T3 can be repeated 2-4 weeks later. Recently it was reported that cats with hyperthyroidism have plasma TSH concentrations (measured with an assay for canine TSH) below the limit of quantification. This offers an additional tool in the diagnostic approach to feline hyperthyroidism. One can also consider testing the suppressibility of plasma T4 concentration in a T3-suppression test.

In hyperthyroid cats, scintiscanning with 99mTcO4− reveals increased uptake in hyperplastic thyroid tissue and no uptake in the unaffected tissue, because TSH secretion is suppressed by the T4 excess. Thyroid scintiscanning is especially useful in hyperthyroid cats in which no thyroid enlargement can be palpated, to determine whether one or both thyroid lobes are affected and whether ectopic hyperfunctioning thyroid tissue (EHTT) is present. Thyroid scintigraphy should be performed preoperatively in all cases.

Treatment
There are four options for eliminating the excess production of T4: (1) radioiodine ablation of the thyroid, (2) surgical thyroidectomy, (3) inhibition of secretion by antithyroid drugs, and (4) an iodine-restricted diet. When the facilities are not a limiting factor, the first option is to be preferred.

Thyroidectomy can best be performed by the modified intracapsular dissection technique. The most serious postoperative complication is hypocalcemia, signs of which appear within 24-72 hours after bilateral thyroidectomy. Oral substitution with L-thyroxine is started in a dose of 50 μg twice daily on the fourth day after bilateral thyroidectomy.
Radioiodine ($^{131}I$) by its β-radiation selectively destroys hyperfunctioning thyroid cells while sparing the suppressed normal thyroid tissue and the parathyroid glands. The normal follicles gradually resume function and there is usually no need for administration of thyroxine. The dose of $^{131}I$ can be determined by a scoring system that takes account of the severity of the signs and symptoms, the size of the thyroid gland(s) (by palpation and/or imaging), and the plasma $T_4$ concentration. From a medical point of view, radioiodine therapy is certainly the most attractive option. With exclusion of preexisting renal disease, the survival time has been reported to be significantly longer in cats treated with $^{131}I$ than in those treated with the antithyroid drug methimazole.

Approximately 5% of treated cats fail to respond completely. If the hyperthyroid state persists for longer than 3 months after the initial treatment, retreatment should be considered, for it is curative in virtually all cases. In less than 5% cats treated with radioiodide, permanent hypothyroidism develops within a few months. Relapse as a result of newly developed nodular hyperplasia in the remaining unaffected thyroid tissue is very uncommon.

Of the available antithyroid drugs, methimazole and carbimazole are most commonly used. Carbimazole is converted to methimazole but yields only half the plasma methimazole concentration as the same dose of methimazole. The doses needed to control hyperthyroidism in cats differ accordingly. The starting dose of methimazole is 2.5 mg per cat twice daily. This can be increased if the response after 2–4 weeks is inadequate.

Side effects have been reported in 18% of cats treated with methimazole and include blood dyscrasias, facial excoriation, hepatotoxicity, and gastrointestinal upsets (anorexia, vomiting). Cats with methimazole-induced blood dyscrasias usually recover within a week of discontinuing the drug. Continued methimazole administration in the presence of thrombocytopenia has led to hemorrhages.

When oral administration poses problems, methimazole can be administered in transdermal formulations. The ointment is applied to the inner surface of the pinna, alternating ears with each dose. The owner is instructed to wear gloves or finger cots for the procedure.

Recently, a iodine-restricted diet (Hill’s Y/D) has been introduced. Its low iodine content results in normalization of the plasma $T_4$ concentration, when the diet is given as the sole food to the animal.

Reference