NON-SURGICAL TREATMENT OF FELINE HYPERTHYROIDISM: OPTIONS AND CONSIDERATIONS

Niet-chirurgische behandeling van hyperthyreoïdie bij de kat: opties en overwegingen

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ABSTRACT

Feline hyperthyroidism is currently the most diagnosed endocrine disorder in cats. It is caused by benign adenomatous hyperplasia of the thyroid gland in 98% of the cases. The two major non-surgical treatment options, administration of antithyroid drugs and radioiodine therapy, are reviewed in this article. Before treatment is initiated, special attention should be given to renal and cardiovascular function. Antithyroid drugs contain thiourylenes, which block the synthesis of thyroid hormones. Therapy should be started at a conservative dose with monitoring of the patient for side effects. Radioiodine is taken up by the hyperactive cells of the thyroid tumor. The decay with emission of β-particles causes local destruction of the surrounding follicle cells. Radioiodine is considered the treatment of choice in most cats.

SAMENVATTING

Hyperthyreoïdie bij de kat is momenteel de meest gediagnosticeerde endocriene aandoening bij de kat. De aandoening wordt veroorzaakt door goedaardige adenomateuze hyperplasie van de schildklier in 98% van de gevallen. De twee belangrijkste niet-chirurgische behandelingen, de toediening van schildklierremmers en de radiojoodtherapie worden in dit artikel besproken. Alvorens met de therapie wordt gestart, verdienen de nierfunctie en cardiovasculaire functie speciale aandacht. Schildklierremmers bevatten thiourylenen die de synthese van schildklierhormonen blokkeren. De therapie dient gestart te worden met een conservatieve dosis en de patiënt wordt voor nevenwerkingen opgevolgd. Radiojood wordt opgenomen door de hyperactieve cellen van de schildkliertumor. Het verval met de uitstraling van β-partikels veroorzaakt een lokale destructie van omgevende follikelcellen. Radiojoodtoediening wordt beschouwd als de beste behandelingsoptie bij het merendeel van de patiënten.

INTRODUCTION

In about 98% of the cases the excessive production and secretion of thyroid hormones causing thyrotoxicosis in feline hyperthyroidism is due to benign adenomatous hyperplasia of the thyroid gland (Meeking, 2005). Thyroid glands of hyperthyroid cats contain single or multiple hyperplastic nodules ranging in size from less than 1 mm to 3 cm in one lobe in +/- 30% of the cases (unilateral affection) or in both lobes in +/- 70% of the cases (bilateral affection) (Holzworth *et al.*, 1980). Occasionally (2%) malignant tumors are observed. The etiology of feline hyperthyroidism is likely to be multifactorial. Environmental factors such as feeding of canned food or the use of cat litter (Kass *et al.*, 1999; Edinboro *et al.*, 2004), overexpression of oncogenes such as c-*ras* (Merryman *et al.*, 1999), and altered G protein expression (Ward *et al.*, 2005) have been associated with the disease. Hyperthyroid cats are usually older than 10 years. Commonly observed clinical signs

Figure 1. Enlarged thyroid nodule of a hyperthyroid cat.

include polyphagia, polyuria, polydipsia, weight loss, behavioral changes like hyperactivity, an unkempt hair coat and gastrointestinal signs. An atypical presentation with the presence of anorexia and lethargy is possible as well, which may be related to the chronicity and severity of the disease (Bucknell, 2000) or an underlying disorder complicating the hyperthyroidism. Clinical signs can be less pronounced when the disease is diagnosed early (Broussard *et al.*, 1995). Clinical examination reveals a palpable cervical nodule (s) in more than 90% of hyperthyroid cats (Thoday and Mooney, 1992; Norsworthy *et al*., 2002). Figure 1 shows a large cervical nodule in a cat diagnosed with hyperthyroidism. Tachycardia and systolic heart murmur are present in 60 and 30%, respectively, of hyperthyroid cats (Thoday and Mooney, 1992). Diagnosis is confirmed by measurement of an increased serum total T4 (TT4) concentration.

Feline hyperthyroidism is currently the most diagnosed endocrine disorder in geriatric cats (Meeking, 2005). It was first reported in cats in 1979 (Peterson, 1979). Therapeutic options include administration of radioiodine (^{131}I) or antithyroid drugs such as methimazole, and thyroidectomy. Each has specific advantages and disadvantages, which are summarized in Table 1. The administration of ^{131}I and thyroidectomy are in principle irreversible methods. The use of antithyroid drugs is reversible. Several factors can influence the choice of therapy. Indeed, preference of the owner, availability of ^{131}I therapy, and the presence of a skilled surgeon are all important considerations. Furthermore, the age of the patient and, more

Table 1. Advantages and disadvantages of treatments currently available for feline hyperthyroidism.

Treatment	Advantages	Disadvantages
Antithyroid drugs	■ inexpensive	■ side effects
	■ no need for surgery, anesthesia or hospitalization	■ need for daily medication and close monitoring
	■ indefinite and reversible	■ not permanent
Radioiodine treatment	■ one treatment	■ need for sophisticated facilities
	■ rapid cure	■ hospitalization time dependant on excretion of radioactivity
	■ no need for anesthesia	
Thyroidectomy	■ relatively easy and inexpensive surgery	■ anesthetic risk
	■ no need for sophisticated facilities	■ possible recidives when not all tissue is removed
		■ complications are frequent

importantly, the presence of concomitant disease such as cardiovascular or renal dysfunction must be taken into account when a therapy is chosen (Kintzer, 1994).

The major non-surgical treatment options available, antithyroid drugs and ^{131}I, will be reviewed in this article.

Special considerations

Special consideration must be given to renal function before initiating any type of treatment. There is a complicated relationship between hyperthyroidism and renal function in cats. Evaluating renal function in a hyperthyroid cat is difficult but important at the same time. First, cats with hyperthyroidism are geriatric patients and in this population chronic renal failure (CRF) is frequently observed. Second, hyperthyroidism can mask CRF. Indeed, hyperthyroidism increases the glomerular filtration rate (GFR), thereby decreasing serum creatinine concentration and BUN. Serum creatinine can also be decreased by the progressive weight loss and reduction in muscle mass observed with hyperthyroidism. A decline in GFR and an increase in BUN and creatinine have been reported as soon as 6 days after successful treatment of hyperthyroidism, regardless of type of therapy (DiBartola *et al*., 1996; Adams *et al*., 1997). Hyperthyroidism may contribute to the development and progress of renal disease by causing hyperfiltration followed by glomerulosclerosis. At present the following recommendations can already be made: a cat presented with hyperthyroidism and mild azotemia, isosthenuria, small irregular kidneys, or proteinuria must be considered at risk of developing renal failure after treatment. The presence of these symptoms pledges for a reversible treatment to evaluate the effect of treatment on renal function before considering any irreversible treatment.

Assessment of cardiovascular function is also important in cats with hyperthyroidism. Cats with hyperthyroidism experience an increased susceptibility to arrhythmias, tachycardia, hypertension, signs of congestive heart failure and ventricular hypertrophy. Hyperthyroidism has a direct effect on the myocardium, vasculature and peripheral tissues, which results in increased myocardial protein synthesis, alteration of myosin subtype, less efficient energy conversion and upregulation of β-receptors (Kienle *et al.*, 1994). Nonselective (propranolol) or selective (atenolol) β-adrenoreceptor blocking agents can be used, if needed, for symptomatic treatment of tachycardia, polypnea, hypertension, hyperexcitability and signs of congestive heart failure. Atenolol has the advantage of requiring a once-daily dosing regimen. In humans, propranolol has the additional effect of inhibiting peripheral conversion of T4 to T3 (How *et al.*, 1980). The pharmacokinetic profile of propranolol is altered by hyperthyroidism. Reduced doses should be given when it is administered orally, and the patient should be closely monitored when making dose adjustments based on cardiac response (Jacobs *et al.*, 1997).

Beta-receptor blocking agents can also be used as an aid in treating hyperthyroidism with antithyroid medica-

Table 2. Important drugs in therapy of feline hyperthyroidism.

Generic name	Classification	Trade name	Indication	Dosage
Thiamazole (methimazole)	Thiourylene	Felimazole®	Hyperthyroidism	2.5 – 5 mg/cat/day
Atenolol	$Beta_1$- (and $Beta_2$ at high doses) adrenoceptor antagonist	Tenormin®	Cardiac arrhythmia, hyperthyroidism, hypertension	6.25 – 12.5 mg/cat PO sid
Propranolol	$Beta_1$- and $Beta_2$ adrenoceptor antagonist	Inderal®	Cardiac arrhytmia's, hypertrophic cardiomyopathy, hypertension, reverse clinical features of thyrotoxicosis	2.5 – 5 mg/cat PO tid
Amlodipine	Calcium channel blocker	Amlor® Norvasc®	Hypertension, hypertensive crisis	0.1 – 0.2 mg/kg PO sid

tion, or alone when antithyroid drugs are not tolerated and the patient is awaiting surgery or ^{131}I treatment. Because they do not act on the thyroid gland itself, they can be given up to the moment of ^{131}I treatment (Mooney, 2001).

A study by Kobayashi (1990) reported an incidence of hypertension in hyperthyroid cats of 87%. A recent study revealed that this percentage of hyperthyroid cats with hypertension at diagnosis has been overestimated in the past and reported an incidence of 12% (Syme and Elliot, 2003). In the same recent study, however, 23% of the initially normotensive cats developed hypertension during the initial 6 months of treatment. The reason for this observation is still unknown, but it clearly points out the need for monitoring blood pressure, even after successful treatment of hyperthyroidism.

Important drugs used in the therapy of feline hyperthyroidism are summarized in Table 2.

TREATMENT WITH ANTITHYROID DRUGS

Mode of action

Thiourylenes are antithyroid drugs derived from a sulfur-containing parent compound called thiouracil. Thiourylenes are actively concentrated in the thyroid, where they exhibit their therapeutic effect by blocking the synthesis of thyroid hormones. More specifically, they block the thyroidperoxidase catalyzed reactions (oxidation of iodide and iodination of tyrosyl residues in thyroglobulin) and the coupling of iodotyrosines to iodothyronines. Thiourylenes also interfere with this coupling by binding to and altering the structure of thyroglobulin. These action sites are shown in Figure 2. Thiourylenes have no influence on the iodide uptake mechanism of the thyroid cell (iodide pump) or the release of previously formed thyroid hormones (Trepanier, 1990; Mooney, 2001).

The most commonly known thiourylenes are methimazole (MMI), a synonym for the pharmaceutical compound thiamazole, and propylthiouracil (PTU). Another agent is carbimazole (CBZ), a carbethoxy derivative of MMI which is not a true thiourylene itself, but an inactive pro-drug. However, CBZ is almost completely bio-activated to an equimolecular amount of MMI after administration. It was developed originally in the search for a drug with a longer duration of activity compared to MMI (Peterson and Aucoin, 1993; Trepanier, 1990). On a molar basis, MMI and CBZ have the same potential, but CBZ has a greater molecular weight, which necessitates a higher dose rate in order to obtain an effect equivalent to MMI. A dose of 10 mg CBZ is approximately equivalent to 6.1 mg of MMI.

In Belgium, only Felimazole® (Thiamazole) tablets of 5 mg are registered for treatment of hyperthyroidism in cats. Methimazole has a bitter taste, but Felimazole® is sugar-coated to simplify administration. Propylthiouracil is very potent in blocking thyroid hormone synthesis but is no longer recommended for use in cats because of severe side effects. These include anorexia, vomiting, lethargy, immune mediated hemolytic anemia and thrombocytopenia (Peterson *et al.*, 1984).

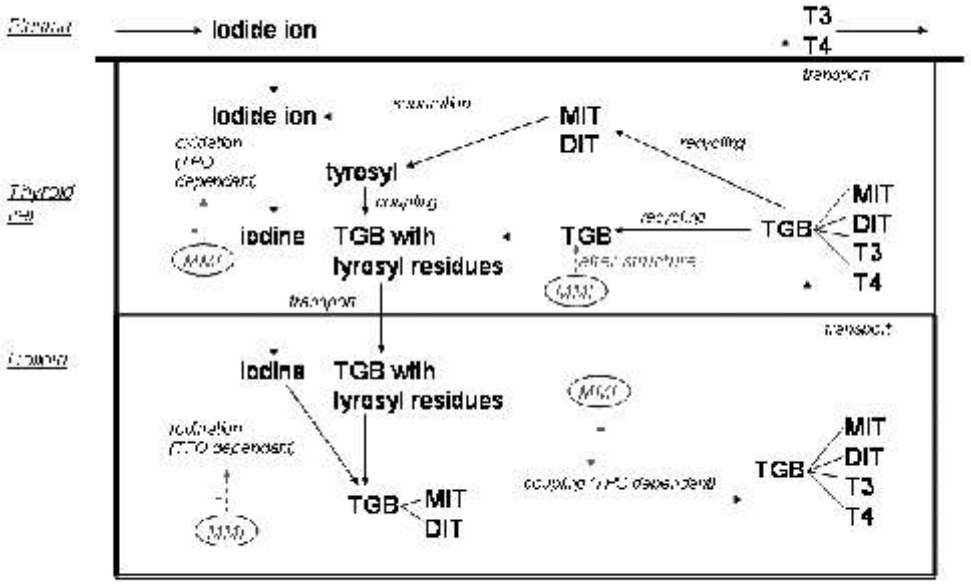

Figure 2. Synthesis of thyroid hormones and action sites of thiourylenes.
MMI: methimazole, TGB: Thyroglobulin, TPO: Thyroid Peroxidase, MIT: mono-iodotyrosine, DIT: di-iodothyrosine
T3: L-tri-iodothyronine, T4: L-thyroxine

Clinical application

The goal of therapy is to maintain serum TT4 concentration in the lower half of the normal range with the minimal dose necessary to achieve this effect. Antithyroid drugs like MMI can be used either as short-term or long-term therapy. Short-term therapy is applicable for patients who need or can benefit from improvement of systemic dysfunctions caused by the hyperthyroidism prior to surgery or ^{131}I treatment, and for patients suspected of chronic renal disease. A euthyroid state will resolve these systemic dysfunctions and will unmask underlying renal failure if present. Long-term therapy with MMI is suited for these patients with unmasked renal failure and for patients for whom surgery or ^{131}I therapy is not advisable and/or accessible. The advantages of long-term therapy are that it requires neither surgical skills nor the availability of ^{131}I treatment. Owners benefit not only from the absence of hospitalization, but also from the spread cost and the ready availability of the drugs compared to surgery or ^{131}I treatment. When treatment with antithyroid drugs is used, the patient rarely suffers from hypothyroidism or hypoparathyroidism, it can receive medication from its owner, and it can be treated up to an old age. This type of therapy is indefinite and any positive or negative effect of the drug encountered by the patient is almost always reversible upon its discontinuation (Kintzer, 1994; Feldman and Nelson, 2004). However, a major drawback of this therapy is the need for daily oral administration, which can be difficult, especially in cats. Antithyroid drugs are not cytotoxic and adenomatous thyroid cells will continue to grow despite the effect of antithyroid drugs. This may require dose adjustments during treatment, which contributes to the need for follow-up (Behrend, 1999).

Dosage

Until a few years ago, the generally accepted protocol for antithyroid drug treatment was a high starting dose of MMI of 10-15 mg/day divided into two or three doses (Peterson *et al.*, 1988) or CBZ 15 mg/day divided in three doses with an 8 hour dose interval (Mooney *et al.*, 1992). Today, these high doses are required in only a small percentage of the patients because cats with hyperthyroidism are diagnosed earlier, when they exhibit less severe symptoms (Broussard *et al.*, 1995). The dose needed depends on the severity of the hyperthyroid state, so after early diagnosis a lower more conservative starting dose can be used with a lower occurrence of side-effects. Currently, 2.5-5 mg/cat/day MMI is the recommended starting dose, with increases of doses if there is an inadequate initial response (Trepanier, 2006).

The clinical signs of euthyroidism become apparent in the patient only after biochemical euthyroidism has been established. Often serum TT4 concentration is below the reference range but there are no signs of clinical hypothyroidism. This can be explained by a relatively high serum free T4 concentration, compared to total T4 concentration. In addition, the concentration of the more metabolically active T3 tends to remain within the reference range (Mooney *et al.*, 1992).

Adverse reactions

Adverse reactions occur in approximately 10-15% of cats treated with a moderate to high dose of MMI (10 to 15 mg/day) (Peterson *et al.*, 1988) or CBZ (15 mg/day) (Mooney *et al.*, 1992). If adverse reactions occur during treatment with MMI, it is almost always in the first 4 to 8 weeks of treatment, which explains the close monitoring needed in that period (Peterson *et al.*, 1988; Trepanier *et al.*, 2003).

The most important clinical side effects during the first weeks of treatment are anorexia, vomiting and lethargy. These are usually transient and may resolve despite continued administration. When the gastrointestinal signs are more severe and persist, an evaluation of the liver function is advised. Apparent hepatic toxicity occurs in less than 2% of cats treated with 10-15 mg/day MMI (Peterson *et al.*, 1988). Hepatopathy is characterized by gastrointestinal signs, icterus and altered serum alanine transferase (ALT) and serum alkaline phosphatase (SAP) concentrations. Hepatopathy requires discontinuation of MMI administration. It will take days or even weeks for all clinical and biochemical problems to resolve and alternative therapies should be considered for further treatment of hyperthyroidism in these cats (Kintzer, 1994).

Another serious clinical side effect is self-induced excoriation of the skin of head and neck, as shown in Figure 3.

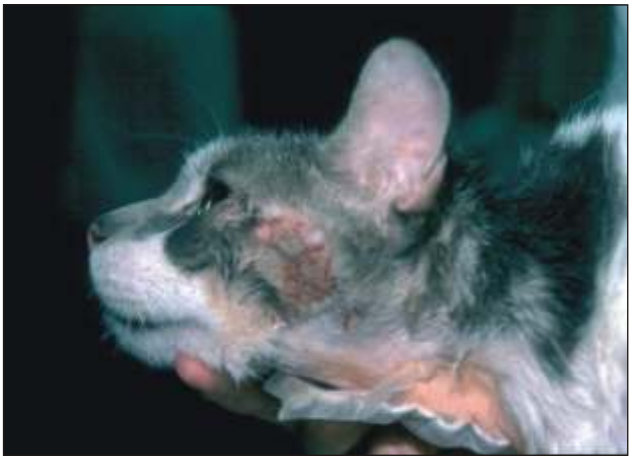

Figure 3. Excoriation of the skin of the head of a hyperthyroid cat treated with MMI.

This side effect requires discontinuing MMI administration, although these cutaneous lesions may be partly responsive to glucocorticoid treatment. Again, alternative therapies for hyperthyroidism need to be considered in these cases (Peterson *et al.*, 1988).

Hematological side effects can be mild, or they can be more serious with need for cessation of therapy. Mild hematological changes occur in 16% of cats treated with MMI. They include lymphopenia, eosinophilia and transient leucopenia (Peterson *et al.*, 1988; Feldman and Nelson, 2004). These can be isolated or related to gastrointestinal signs. More serious side effects occur in approximately 3% of cats treated with MMI (Peterson *et al.*, 1988). These include severe thrombocytopenia associated with a bleeding tendency, and agranulocytosis associated with fever, anorexia, lethargy and localized or systemic infections. Relatively rare but serious side effects include immune mediated hemolytic anemia (IMHA) with a positive Coombs' test, and coagulopathy, which is unassociated with thrombocytopenia. Cats with coagulopathy and a normal platelet count can have a prolonged 'proteins induced by vitamin K absence or antagonists' (PIVKA) clotting time (Randolph *et al.*, 2000). Some hyperthyroid cats may already have abnormal coagulation profiles prior to treatment. In the study by Randolph *et al.* (2000), 3 cats (n=20) had 1 or more abnormal coagulation test at the onset of the study, although none had evident bleeding tendencies. The cause of this is not known, but it is speculated that decreased vitamin K absorption associated with the fat malabsorption seen in some hyperthyroid cats resulted in abnormal pretreatment PIVKA clotting times. These serious side effects require the discontinuance of MMI therapy and supportive care such as intravenous fluids, blood transfusions and/or antibiotic therapy. In the study by Peterson *et al.* (1988), more than 50% of the cats treated with MMI for longer than 6 months developed positive antinuclear antibody (ANA) test results. The risk for ANA's appears to increase with longer duration of MMI treatment and with higher daily doses of MMI. The importance of these findings is unknown, since none of the cats from this study showed any signs of a lupus-like syndrome.

The side effects related to CBZ therapy are similar to those related to MMI therapy (Mooney, 1998; Behrend, 1999; Bucknell, 2000). In CBZ treated cats, 10% have mild side effects with vomiting occurring within the first 3 weeks of therapy, with or without anorexia and lethargy. Carbimazole is tasteless (Cooper, 1984), which may account for the lower incidence of vomiting.

In 5% of the cases treated with CBZ, mild and transient lymphopenia, eosinophilia or leucopenia occurs, without the need for discontinuation of therapy. Excoriations of the skin are described rarely and occur during the first 6 weeks of treatment, along with the need for discontinuation of therapy. More serious side effects like agranulocytosis or thrombocytopenia have not yet been described for the use of CBZ, but the possibility of developing these side effects may still exist (Mooney, 1998; Bucknell, 2000), therefore monitoring is still advised. Mooney *et al.* (1992) suggested that the incidence of adverse reactions using CBZ compared to MMI is lower. However, the number of cats included was small and a low dose regime was used in this study (Mooney *et al.*, 1992).

Side effects are less frequent and less severe at relatively low MMI doses of 2.5-5 mg/day compared to the relatively high doses of 10-15 mg/day. When MMI is started at 2.5 to 5 mg/cat/day, adverse reactions are seen in only 5% of the cats treated (Chapman *et al.*, 2005). The following protocol is suggested in the literature to control hyperthyroidism gradually with minimal occurrence of side effects (Mooney, 1998; Chun *et al.*, 2002; Feldman and Nelson, 2004). A trial therapy for 4 weeks is started with a recommended initial dose of 2.5 mg MMI twice a day for 2 weeks. After 2 weeks the owner is contacted for follow-up about side effects. When no side effects are reported, the dose should be increased to 3.75 mg twice a day for an additional two weeks. After this trial period, the veterinarian is consulted for a complete history, physical examination and blood work, including hematology, serum biochemistry and serum TT4 concentration. According to these results, three different therapeutic decisions can be made, depending on the serum TT4 concentration. First, serum TT4 concentration can be within or near the normal reference range. The dose is then best maintained for another 2 to 6 weeks, after which the veterinarian is consulted for examining the patient and determining the need for a further dose adjustment. Secondly, if after this initial 4 week trial period the serum TT4 concentration is below the reference range, the dose must be reduced by 25% to 50% and the cat must be rechecked 4 to 8 weeks later. Finally, if the serum TT4 concentration 4 weeks after initiating therapy is still above reference range, the dosage should be increased every 2 weeks by 2.5 mg per day, to a maximum of 20 mg/day. Most cats will be controlled with a dose of 5 or 7.5 mg/day (Peterson *et al.*, 1988). Nonetheless, this effective dose requirement varies between cats. With this low-dose protocol, clinical improvement may be delayed, occurring 2-6 weeks after normalization of serum TT4 concentration. Tablets of 5 mg MMI (Felimazole®) should not be divided into smaller doses due to the coating. Therefore initial therapy is often started with a dose of 5 mg once a day.

The serum half life of MMI in cats is only in the range of several hours after oral administration (Trepanier *et al.*, 1991), but MMI may possibly be concentrated in the thyroid gland in cats as it is in humans, which leads to prolonged antithyroid effects (Okuno *et al.*, 1987). It has recently been demonstrated that once daily therapy is adequate in many cats but that twice daily administration of MMI leads to a good control of the hyperthyroidism in a larger number of cats (Trepanier *et al.*, 2003).

A different low-dose protocol is advised when CBZ is used. In this case it is recommended to give 2.5 mg twice a day for 7 days and then 5 mg twice a day for 3 weeks. After this period, the veterinarian needs to be consulted for the same assessments as for MMI after the 4 week trial period, and dose adjustments can be made if necessary (Feldman and Nelson, 2004). Nonetheless, for long-term treatment of hyperthyroid cats, a regimen of 5 mg twice a day is recommended (Mooney *et al.*, 1992; Mooney, 1998).

A trial therapy with antithyroid drugs prior to a definite treatment such as ^{131}I or surgery is needed when concurrent renal insufficiency is suspected. A lower starting dose of 1.25 mg once or twice daily is advised in cats having or suspected of having renal disease. The dosage can be increased as described earlier with special attention to renal parameters such as serum creatinine and phosphor concentration, and urinalysis. When the renal function is not decreased after euthyroidism is achieved, medication can be continued with monitoring for occurrence of possible side effects, or a definite treatment such as ^{131}I can be considered. However, when the renal function decreases to the point where renal failure becomes clear, it can be beneficial to continue MMI administration at a lower dose. In this situation mild hyperthyroidism is maintained, which favors the renal function (Feldman and Nelson, 2004).

Long-term treatment

Once hyperthyroidism is controlled, a long-term dosing regimen can be designed, which involves monitoring the cats every 3 to 6 months. After the initial 3 month period, side effects are uncommon, but can still occur. Because thiourylenes only control the disease up to a certain point and tumor cell growth continues, dose adjustments are likely to be necessary. Another important issue during long-term therapy is owner compliance. Poor owner compliance can be due to impractical time schedules for the owner, a cat that is difficult to pill or simply an unwilling owner. A solution for this can be to reduce the frequency of administration but to maintain the same total daily dose of MMI. In this case it is important for the owners to closely observe their cats for the possible gradual return of clinical signs.

Because cats can be difficult to pill, several other methods for MMI administration have been investigated. Transdermal MMI administered in a topical gel is one option (Hoffmann *et al.*, 2003; Sartor *et al.*, 2004). Therapeutic response is seen after 4 weeks, which is longer than with the use of oral MMI, and may not even occur in every cat. The hepatic and hematologic side effects and pruritus are equal to that with oral MMI, but cats can experience crusting and erythema of the pinnae of the ear where the drug is applied. Just as with the oral MMI, a low dose trial therapy is advised with a starting dose of gel equal to 2.5 mg MMI applied twice daily (Sartor *et al.*, 2004). The owner must wear gloves when rubbing the gel in on alternating ears, with any excess removed after 30 to 120 minutes. The disadvantages of this form of treatment are the relatively high cost and the trial stage this form of treatment is still in. In one study, the use of transdermal MMI led to significantly fewer gastrointestinal side effects compared to oral administration. There was, however, no difference in the incidence of hematological abnormalities, hepatopathy or facial excoriations. Veterinarians must be warned about the variable types of creams and methimazole used by the compounding pharmacies, with implications for its use. Another option, although not thoroughly investigated, is the parenteral way for administration of MMI (Sassnau, 1999). The administration of MMI, in the same dose as advised when administered orally, was in some cases experienced as a beneficial route with advantages compared to oral administration. Overall, when a cat is difficult to pill, the best treatment option is administration of ^{131}I.

TREATMENT WITH RADIOACTIVE IODINE (RADIOIODINE, ISOTOPE ^{131}I)

Principle of therapy

Administration of ^{131}I can be intravenous (IV), subcutaneous (SC) or oral (Behrend, 1999; Mooney, 2001). Thyroid cells actively take up stable or radioactive iodine and incorporate it into tyrosyl groups during thyroid hormone synthesis. Hyperplastic or tumoral thyrocytes are hyperactive and will take up more ^{131}I as opposed to healthy cells. Uptake of ^{131}I by normal cells is suppressed due to the negative feedback system on the hypothalamic-pituitary-thyroid axis. Radioiodine undergoes β decay and emits β-particles and γ-radiation. The β-particles travel a maximum distance of approximately 2 mm, during which they cause local destruction of the surrounding follicle

cells. Surrounding structures, such as the parathyroid and healthy suppressed thyroid cells, are spared (Mooney, 2001; Feldman and Nelson, 2004). The γ-radiation penetrates the tissue, is less radiotoxic than the β-particles, and permits imaging with the γ camera. Iodine not taken up by the thyroid is excreted in saliva and urine, and through the gastrointestinal system.

Follow-up after ^{131}I therapy is very important. It is recommended to measure serum TT4, creatinine and BUN after ^{131}I therapy. An example of a follow-up schedule is monitoring 1, 3 and 6 months after ^{131}I therapy. When cats have a low serum TT4 concentration 1 month after treatment, it is possible that healthy reactivated cells are not yet producing enough thyroid hormones. This production usually increases hereafter and euthyroidism is achieved 3 to 6 months after ^{131}I.

Before treatment, a scintigraphic scan of the thyroid using pertechnetate ($^{99m}TcO_4$) should be performed to investigate whether there is uni- or bilateral involvement of the thyroid lobes, and whether there is a presence of ectopic thyroid tissue or signs of malignancy. Pertechnetate is trapped by the thyroid gland in the same way as iodide but is not organified by the thyroid gland. It decays with γ radiation, enabling visualization with a γ camera.

In rare cases the thyroid pathology can be malignant (adenocarcinoma). Adenocarcinoma gives non-homogenous uptake on the pertechnetate scan, however it can only be confirmed by histology. Adenocarcinoma is treated with a higher dose of ^{131}I of 10 tot 30 mCi (Peterson, 2000).

Dose assessment

The ultimate goal of the treatment of adenomatous hyperplasia is to restore the euthyroid state with a single dose of ^{131}I, without developing hypothyroidism or recurrence of hyperthyroidism. A variety of methods to assess the optimal dose of ^{131}I have been investigated. These methods can be divided into three groups, being a tracer study combined with $^{99m}TcO_4$, a scoring system, or administration of a fixed dose.

Tracer study combined with $^{99m}TcO_4$

This dose assessment uses the kinetic parameters and volume of the thyroid gland (Turrel *et al.*, 1984; Meric *et al.*, 1986; Theon *et al.*, 1994). A tracer study using a low dose of 100-300 μCi ^{131}I is performed. During 3 to 5 consecutive days after injection, a scintigraphy is performed from which the uptake and the residency time of ^{131}I in the thyroid (biological half life) are calculated. To estimate the volume of the thyroid gland, the cat is injected with $^{99m}TcO_4$ and a scintigraphy is performed after 1 hour. Specific algorithms are used to quantify the volume of the affected thyroid. The goal of this dose assessment is the calculation of the amount of ^{131}I activity (mCi ^{131}I) to be injected IV to achieve a radiation dosage of 150 Gray (Gy) in the thyroid. This assessment of dosage has the disadvantage of the need for repeated sedations, which is not advisable in a geriatric population such as hyperthyroid cats.

Scoring system

A scoring system based on the severity of the clinical symptoms, size of the thyroid and serum TT4 concentration is described in Jones *et al.*, 1991; Mooney, 1994; and Nykamp *et al.*, 2005. Based on this scoring system, 3 dose rate regimes can be used: a low dose of ^{131}I of 2-3.5 mCi IV, a moderate dose of 3.5-4.5 mCi IV and finally a high dose of 4.5-6.5 mCi IV (Peterson and Becker, 1995). The advantages of this method are that less time is required because no tracer studies are performed, and that no sedations are necessary.

Fixed dose of ^{131}I

For administration of a fixed dose, a difference is made between a moderate dose of 4 mCi and a very high dose of 10-30 mCi. A dose of 10 to 30 mCi will not only destroy the adenomatous tissue, but the healthy tissue as well. This will lead to an unacceptably high number of hypothyroid cats after treatment with a high cost price, as well as high exposure to radiation for the environment. A fixed dose of 4 mCi can be administered with (Chun *et al.*, 2002) or without (Meric and Rubin, 1990) performing a $^{99m}TcO_4$ scan previous to ^{131}I. When a $^{99m}TcO_4$ scan is performed and the fixed-dose of ^{131}I is chosen within a range according to the outcome of the scan, the method is called the 'modified fixed-dose' method (Forrest *et al.*, 1996).

Route of administration

There is no difference between IV or SC administration for efficacy of treatment, hospitalization period, ^{131}I uptake by the thyroid or ^{131}I excretion (Theon *et al.*, 1994). Subcutaneous administration gives a risk for radiation induced dermatitis. For the oral administration route, a higher dose is needed compared to the IV or SC route, with increased risk during treatment for the environment caused by vomiting or biting the capsule (Malik *et al.*, 1993; Forrest *et al.*, 1996). Therefore, the oral route is not advised in cats.

Table 3. Results of treatment with ^{131}I using different types of dose assessment in hyperthyroid cats.

Method of dose assessment	Dose ^{131}I administered (mCi)	N (number of cats)	Follow-up (months)	% hyperthyroid (n)	% hypothyroid (n)
Tracer study					
(Turrel *et al.*, 1984)	1-5.9	11	6-18	27 (3)	18 (2)
(Meric *et al.*, 1986)	1.5-6.13	31	1	10 (3)	7 (2)
(Theon *et al.*, 1994)	3.6	120	15-56	4.17 (5)	6 (7)
Scoring system					
(Jones *et al.*, 1991)	1.1-2.7	32	3-4	9 (3)	3 (1*)
(Mooney, 1994)	2.16-5.4	50	3-32	10 (5)	56 (28) after 1 month 14 (7) after 15 months
(Peterson and Becker, 1995)	3-5	524	every 3-6 months	2.5 (13) after 3 months 1.6 (8) after 6 months	16 (84) after 3 months 11 (57) after 6 months 2.1 (11*) after 1.6 years
(Nykamp *et al.*, 2005)	3.5-24	165	3-60	Not reported	30 (50) (23*)
Fixed dose					
(Meric and Rubin, 1990)	4	60	1-28	8 (5)	8 (5)
(Forrest *et al.*, 1996)	2-5**	80	1-51	9 (11)	Not reported
(Chun *et al.*, 2002)	4	193	12	1 (2)	9 (19*)

n: number of cats
*supplemented with thyroxine because of clinical signs of hypothyroidism.
**according to scintigraphic $^{99m}TcO_4$ scan

Radioprotection

After the administration of ^{131}I, the cat must be considered a source of radioactive radiation and radioprotective precautions must be taken. The advised period of hospitalization depends on national legislation and shows some variation from country to country. In Belgium, the release limit is patient emission of less than 20 µSv/hour at a distance of 1 meter. No clinical parameters allow prediction of the hospitalization period required (Weichselbaum *et al.*, 2003). With the injected dose used in our settings, the cat is already below this limit at 24 h after injection. Nevertheless, the cats are hospitalized for a longer time because during the first 72 hours the highest radiation burden is achieved in urine and feces due to the elimination of free radioiodine. After an average hospitalization period of 5 days, by which time the dose tempo is usually less than 20 µSv at a distance of 1 meter from the cat, the patient can go home with safety precautions. For a period of two weeks, there must be no contact between the cat and little children or pregnant women, though limited contact with the rest of the household is allowed. All material that was in contact with the cat or its excrements, including litter box filling, must be kept separate for a time period of three months (this is 10 times the physical half-life of ^{131}I, after this time <0,1% of the initial radioactivity is left) until it can be disposed as normal waste.

Outcome of ^{131}I treatment

The outcome depends on the method of dose assessment, age at time of diagnosis and sex (Slater *et al.*, 2001). Possible factors influencing prognosis are the administration of MMI previous to ^{131}I (Chun et al., 2002; Nieckarz and Daniel, 2001) and bi- or unilateral involvement of thyroid lobes (Nykamp *et al.*, 2005). The success

of treatment is not significantly correlated to symptoms before treatment such as the presence of weight loss, polyuria, polydipsia, behavioral changes, anorexia, vomiting, cardiac murmur or tachycardia (Chun *et al.*, 2002).

The results of treatment using the different types of dose assessment described in the literature are outlined in Table 3.

Slater *et al.* (2001) has shown that each year of higher age at diagnosis increases the relative risk to die within two years after treatment, since the increasing number of health problems in the old cat diminishes the survival time strongly. These findings are not surprising, since hyperthyroidism is a disease of geriatric cats. Also, it is reported that male cats have a poorer survival rate over time with a higher risk of dying within two years after diagnosis and treatment, compared to female cats diagnosed and treated at the same age. Other important predictive factors for survival are renal failure and neoplasia after treatment.

The effect of antithyroid drugs on ^{131}I therapy remains controversial. Methimazole does not inhibit thyroidal iodine uptake, but the administration of MMI without discontinuation before ^{131}I therapy is currently not recommended. It lowers the effective half-life of ^{131}I by inhibiting incorporation of iodine in tyrosyl groups and lowering the residence time of ^{131}I in the thyroid. Nonetheless, there is a short rebound effect with enhanced iodine uptake after recent MMI withdrawal in healthy cats (Nieckarz and Daniel, 2001). This rebound effect can be potentially beneficial in ^{131}I therapy of hyperthyroid cats. Despite this, a recent study has shown that discontinuing MMI for less than or more than five days prior to ^{131}I therapy has no effect on treatment outcome (Chun *et al.*, 2002). It can be reasonably advised to cease MMI administration three days prior to ^{131}I treatment.

A bilaterally enlarged thyroid gland may be a higher risk for developing hypothyroidism after treatment compared to a unilateral enlargement, because both thyroid lobes in the bilateral enlarged thyroid gland take up ^{131}I, while in a unilateral enlargement one lobe is suppressed and does not take up ^{131}I (Nykamp *et al.*, 2005).

Overall, the treatment of feline hyperthyroidism with ^{131}I should be considered the treatment of choice. In the majority of cases, one treatment is sufficient. This procedure is only minimally stressful to older cats, requires no anesthesia, has a very low complication rate and leads to a rapid cure of the disease. Nonetheless, the use of radioactive material requires hospitalization, specialized facilities and personnel, and can be a menace for the environment when radioprotective safety precautions are not taken (Kintzer and Peterson, 1994; Meeking, 2005). Before initializing an irreversible treatment like ^{131}I, the renal function should be carefully evaluated. When a cat is presented with hyperthyroidism and suspected of underlying kidney failure, a trial period with anti-thyroid drugs previous to ^{131}I can give insight into the development of CRF after therapy.

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