Feline hyperthyroidism – part two: evidence-based medicine

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ANDREW L BODEY BVSc, CertVR, MRCVS reviews evidence for some of the treatment options utilised for feline hyperthyroidism in the UK

FELINE hyperthyroidism is the most commonly identified endocrine disorder in cats aged 10 or older, caused in approximately 95 per cent of cases by functional thyroid adenomas varying in diameter from 1mm to 30mm.

Between 70 per cent and 75 per cent of these adenomas are bilateral, and up to 20 per cent of them are ectopic (intrathoracic). Carcinomas account for fewer than five per cent of cases. As discussed in part one of this article (*VT*44.29), strategies for preventing feline hyperthyroidism are of unknown efficacy and, currently, treatment options are long-term management or cure (**Panel 1**).

Up to 10 per cent of older cats may be subclinically hyperthyroid. Clinical findings include weight loss, polyphagia, hepatopathy, tachycardia, reduced coat quality, polydipsia, polyuria, diarrhoea, vomiting, secondary left ventricular hypertrophy, and restlessness/aggression.

If left untreated, hyperthyroidism will shorten lifespan through congestive heart failure, thromboembolic disease, behavioural change (for example, manic behaviour may predispose to accidental injury) or other consequences. This article reviews the evidence base for the treatment options discussed, featuring in **Panel 1**.

Medication

All licensed and unlicensed medications rely on the prescribed drug being metabolised to the

physiologically active form, methimazole, and will be discussed together, although differences in formulation influence the overall efficacy.

Methimazole is efficacious in suppressing total thyroxine (T_4) to euthyroid ranges, through its action on thyroid peroxidase (the same mechanism as the goitrogens in soy protein; see part one). Since the enzyme blockade is rapid (when an appropriate dose is achieved), the time to reaching euthyroidism reflects the body's stores of T_4. Euthyroidism is usually achieved within two to three weeks, dependent on client compliance and cat tolerance of adverse effects. Similarly, cessation of medication results in a return to hyperthyroidism as rapidly as within two days (Peterson et al, 1988).

In its various formulations, methimazole is readily available in the UK and is the preferred choice of 65.7 per cent of 603 UK general practitioners (Higgs et al, 2014), with the added advantages of flexibility of dose levels, the ability to reduce or discontinue medication in the presence of azotaemia, and the fact its effects are reversible. However, adverse effects to methimazole have long been recognised, as summarised in **Panel 2**. In addition, methimazole is a potential teratogen in man; clients should not split or crush tablets, and should handle litter trays with gloves.

Side effects were seen most often within one to two months of the medication commencing, although vigilance following a dose increase is advisable. Adverse effects reported more recently include generalised lymphadenomegaly (Atkinson, 2008), vasculitis with digital and tail necrosis, and renal infarcts (Bowlt et al, 2013).

Methimazole can also induce hepatopathy. It is for these reasons manufacturers recommend frequent blood monitoring, for example at three, six, 10 and 20 weeks after starting, and then every 12 weeks. In the author's experience client compliance with this regime is often lacking and, in the event of unexplained ill-health, instigation of prompt haematology and biochemistry is advisable, regardless of whether a monitoring programme is in place. As shown in **Panel 2**, some adverse effects are dose dependent, and it might be expected the current use of lower starting doses may avoid many of those first reported. However, **Panel 2** also summarises practitioner experience in the UK, and describes many adverse effects as still being widely observed (Higgs et al, 2014).

In early work, Peterson (1988) described the following outcomes with oral methimazole, when using a starting daily dose of 10mg to 15mg. At two to three weeks, 35 per cent of hyperthyroid cats became hypothyroid, while 12.6 per cent remained hyperthyroid. During long-term follow-up, exceeding 100 days, the mean total T_4 for the test population was within reference intervals at all points. However, from nine sampling occasions, 32.8 per cent of cats were hyperthyroid on one to four occasions, and 46.8 per cent were hypothyroid on one to three occasions. Dose adjustments were made in increments of 2.5mg to 5mg, with the aim to achieve euthyroidism within the lower half of normal range. These data suggest control is good for a population of hyperthyroid cats, with mean T_4 remaining within the reference interval at each sampling point, but individual control difficult to achieve reliably. Clients in the study judged their cats' clinical responses to be fair to

excellent.

Respondents to an online survey of client experience with oral medication (Caney, 2013) reported medication “helped a lot” or “cured” 75 per cent of cats on methimazole (Felimazole, Dechra), and 72.2 per cent of those on carbimazole (Vidalta, MSD). Overall reliability of medicating was reported as at least 75 per cent, with 51.4 per cent of clients having no difficulty medicating their cats. The remaining 48.6 per cent of clients had difficulties daily, weekly or monthly in ensuring their cats were medicated, and pill pockets were reported as the most helpful medicating aid. Tablet crushing was reported as the least helpful, and this also suggested awareness of appropriate tablet handling was not universal.

As a long-term treatment plan, up to 25 per cent of clients were unable to reliably medicate their cat. This is important, as 98 per cent of UK GPs cited owner compliance with medications as a deciding factor in their long-term management planning (**Panel 3**; Higgs et al, 2014).

By contrast, transdermal methimazole gel was reported as easy to apply for 96.7 per cent of clients in a study (Boretti et al, 2013), with overall regular application achieved for 83.4 per cent of cats. Reasons offered by the 16.6 per cent of clients not achieving regular application included owning “outdoor” cats, being absent on holiday and observing no apparent deterioration when medication was missed, hence it being discontinued. Side effects were not widely observed but included predominantly pinnal dermatitis, which could develop many months after starting.

Clinical outcome, as with oral methimazole, indicated good population control, with the mean T_4 of the group always within reference intervals. A very wide variation around the mean was noted, so many individuals had poor control, becoming either hypothyroid or remaining hyperthyroid. The authors demonstrated time of sampling in relation to medication did not influence the measured T_4, and suggested wide variation was perhaps caused by insufficient regularity of application, changes in thyroid tumour size, non-thyroidal illness and pharmacological variations in the unlicensed gel.

In a separate paper (Milner et al, 2006), mean survival time for cats treated with methimazole was found to be two years (range 1.0 to 3.9), and four years for cats treated with radioiodine treatment (range 3.0 to 4.8). No difference in the pre-treatment groups was identified, with renal and hepatic function similar between the groups. The authors reported the mode of treatment was the only factor affecting outcome, and suggested possible factors for the shorter lifespan for the methimazole group included difficulty in medicating and the effect of methimazole toxicoses.

These suggestions are supported by findings by Caney (2013), Peterson (1988) and Higgs (2014). Boretti (2013) speculated “inconsistent T_4 concentrations with extremely high variations between the testing intervals could be a possible explanation for the observed shorter survival time [of cats on methimazole] compared with radioiodine treated cats”. Milner et al (2006) reported their study population as having only a small bias compared with the population of hyperthyroid cats at large, indicating they felt their findings had wide relevance.

Iodine-depleted diet

The recommended inclusion rate for iodine is given as 0.5ppm to 2ppm (Peterson, 2012a). When hyperthyroid cats are fed an exclusive diet containing 0.14ppm or 0.19ppm (Hill's y/d, canned and dry respectively), total T_4 can return to the reference interval, with 90 per cent of cats becoming euthyroid after 12 weeks of exclusive feeding (Melendez, 2012).

Like methimazole, life-long use is required, with a rapid return to hyperthyroidism if some other diet is included. Although adverse effects have not been reported, periodic monitoring of total T_4, biochemistry, urinalysis and clinical examination is recommended at four, eight and 12 weeks, and then every 26 weeks after transitioning the diet. Feeding iodine-restricted diets to euthyroid cats predisposes to the development of hyperthyroidism (*VT*44.29).

A prospective trial of 225 cats (van der Kooij et al, 2013) fed Hill's y/d, whose total T_4 was measured four and eight weeks after starting the diet, reported euthyroidism in 68 per cent and 75 per cent of the cats they measured, respectively. However, of the 225 cats starting the trial, only 88 and 68 were measured at four and eight weeks, respectively, and, overall, euthyroidism was achieved in 25 per cent and 23 per cent of the starting population at four and eight weeks, respectively. The authors cite poor palatability of the diet as the main reason for the lack of cats available for testing at four and eight weeks. Interestingly, differences in total T_4 between four and eight-week samples, and between "indoor" and "outdoor" cats, were not statistically significant.

Use of methimazole and iodine-depleted diet concurrently was not recommended, because of one case of subclinical hypothyroidism. Iodine does have physiological roles unrelated to T_4, and the authors suggested their trial was too short to exclude the possibility of adverse effects from long-term use of the depleted diet. Peterson (2012b) has expressed concern as to the suitability of y/d as a long-term diet.

Surgery

For the anaesthetist, challenges relate to the older age group typical of the condition, with tachycardia a common occurrence. Hypokalaemia and subclinical bacterial cystitis commonly occur and should be screened for. For the surgeon, challenges include the presence of micro as well as macroadenomas (microadenomas being difficult to visualise), the potential for iatrogenic parathyroid damage resulting in potentially life-threatening hypocalcaemia, up to 20 per cent of cases possibly having intrathoracic ectopic thyroid tumours and 70 per cent to 75 per cent of cases having bilateral thyroid disease.

All this means the surgical process often requires repetition, or a single bilateral thyroidectomy when parathyroid damage becomes more likely. However, with an appropriate anaesthetic regime, experienced surgeons can achieve a low incidence of surgical complications. Surgery "is an effective treatment for hyperthyroid cats when radioactive iodine therapy is not available" (Naan et

al, 2006).

Radioiodine treatment (RIT)

Iodine 131 is a dual emitter of beta and gamma radiation, and is typically administered as a subcutaneous injection. In uncontrolled hyperthyroid patients, it is taken up preferentially by thyroid tumour, and normal thyroid tissue, being dependent on thyroid-stimulating hormone (TSH), is usually spared. The path length of the beta radiation is approximately 600nm, and no reports of side effects, including damage to the parathyroid glands, have been noted.

Gamma radiation is the same as x-ray radiation and carries the same challenges for radiation safety, with the additional complications radiation continues until, following a half-life curve, background radiation is reached (typically five to six weeks post-treatment). Excreta from treated cats also presents a radioactive contamination hazard. Highest hyperthyroidism cure rates can be achieved using higher doses, whereas a lower incidence of iatrogenic hypothyroidism post-treatment follows lower doses.

Radioiodine doses can be given as a fixed dose or as an individualised dose, either following scintigraphy or an estimate of individual clinical need. Clinical outcomes are best with an individualised dose, with scintigraphy achieving only the same results as the clinical need estimation (Puille, 2011).

Many tumour cells are killed outright, but some are simply damaged, becoming unable to divide; hence, the full effect of radioiodine may not be seen until up to six months post-treatment. **Panel 4** summarises some outcome data.

Around 1.5 per cent of cases require a second treatment if the cat is still hyperthyroid six months post-treatment, but carcinoma is suspected for those still hyperthyroid after two treatments. Identifying the tumour type definitively before treatment is hampered by up to 20 per cent of cases being ectopic, and it is known that both benign and malignant forms can be found in the same thyroid lobe, making fine-needle aspiration biopsy unreliable (Hibbert et al, 2009). Carcinoma patients respond best to much higher doses of RIT, available, for example, at the University of Bristol.

Client perception of RIT in Caney's survey was that 100 per cent of clients thought it had "cured" their cat or "helped a lot". A more recent survey (Boland et al, 2014) reported 91.7 per cent client satisfaction with RIT, but the authors suggested the lower level may reflect their lower outcome success of 81.4 per cent, resulting from their use of a fixed low-dose schedule at that time.

RIT has no side effects, but, in the event of patient ill-health, access is severely restricted, at least immediately post-treatment. Like radiography, work with unsealed ionising radiation must be undertaken in a controlled area, and treated cats cannot leave it until, and unless, discharge criteria

are met. Although these may vary between centres, in practice it makes routine diagnostic and treatment equipment unavailable during this period, and a routine blood sample requires a risk assessment, both for sampling and for processing a radioactive sample. Hence, each UK centre will have a pre-referral protocol, with the intention of excluding unsuitable patients where ongoing concomitant disease would be difficult to manage.

In the author's experience, the social separation of cats from owners can sometimes result in temporary inappetence, but this is helped substantially by minimising the hospitalisation period (in the UK, cats can return home from seven days post-treatment) and by providing spacious behaviourally enriching environments that include scratching posts, hiding places, separate feeding and toileting areas, off-floor areas, and natural daylight (Figure 1). This is important because clients express more concern about the hospitalisation period than any other factor (**Panel 3**).

Pre-referral investigation will vary between centres. Diagnosis is required with total T_4; free T_4 is less susceptible to non-thyroidal illness. An elevated free T_4 while T_4 remains within normal range, suggests either an early clinical diagnosis or suppression of total T_4 because of non-thyroidal illness. Use of an external laboratory allows a diluted sample to be retested, if the initial result lies outside its reporting interval.

Haematology, biochemistry and urinalysis, including specific gravity (SG), urine protein creatinine (UPC) and bacteriology (if it is a cystocentesis sample), form an important benchmark, and the degree of imaging and additional information required will vary between clinical cases and centres.

Use of pre-referral trial treatment to confirm renal parameters within reference intervals while total T_4 is in the lower half of reference intervals has been routine in the UK, but is not a requirement at all treatment centres. It is important to monitor renal parameters and T_4 following RIT, as iatrogenically hypothyroid cats are more likely to develop azotaemia, and azotaemic hypothyroid cats have approximately half the life expectancy of cats without it (Williams et al, 2010).

Maintaining azotaemic cats in a mildly hyperthyroid state by partial control with methimazole has been recommended (the enhanced glomerular filtration rate resulting from mild hyperthyroidism offsetting the azotaemia), but this may increase morbidity and reduce survival by promoting progression or development of chronic kidney disease and provoking cardiac remodelling. It is regarded by some as an outdated recommendation (Higgs et al, 2014). Cats that are azotaemic at the time of diagnosis can still benefit from RIT, when a temporary supplementation with T_4 cushions the kidneys against the hypothyroidism sometimes encountered immediately post-treatment (Broome and Peterson, 2013).

Life expectancy was discussed earlier, but not all authors have repeated those findings (Slater et al, 2001; Peterson and Becker, 1995).

However, given most cats are middle-aged to elderly at the time of treatment, Peterson concludes:

"… the limiting factor in survival time for most cats with hyperthyroidism treated with radioiodine is not the disease itself or the treatment, but simply old age."

Logically, using radioiodine at the point of diagnosis, rather than the point of medication intolerance or bilateral thyroidectomy failure, will offer the maximum benefit to the patient.

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Panel 1. UK feline hyperthyroidism treatments

Management

Iodine-restricted diet

• Hill's y/d (dry or wet)

Medication – oral

• Methimazole – Felimazole (Dechra Veterinary Products), 1.25mg, 2.5mg, 5mg

• Carbimazole – Vidalta (MSD), 10mg, 15mg

• Thiamazole – Thiafeline (Animalcare), 2.5mg, 5mg

Medication – transdermal

• Methimazole – available off-licence as Methimazole Transdermal Gel (Summit Veterinary Pharmaceuticals)

Cure

Thyroidectomy

• Uni or bilateral, single procedure or staged, thoracotomy required for ectopic

Radioiodine

• Single or staged double-dose treatment

• High-dose treatment for thyroid carcinoma

Other

Described in the literature, includes:

• Homeopathy – one report claims successful resolution of clinical signs in a series of four cases (Chapman, 2011)

• Ultrasound-guided heat ablation – one study of nine cats found this an effective temporary treatment with total T_4 returning to the reference range (Mallery et al, 2003)

Panel 2. Reported adverse effects to oral methimazole in a clinical trial, and experientially among UK general vets

Of 262 cats, in the first one to two months of starting medication, adverse effects were typically observed in the percentage of cats shown (Peterson et al, 1988):

• Anorexia, vomiting, lethargy, excoriation of face and neck, **BLEEDING**, hepatopathy – 18.1%

• Eosinophilia, lymphocytosis, leukopaenia (can be **SEVERE** or mild) – 16.4%

• Agranulocytosis, **THROMBOCYTOPAENIA** – 3.8%

• Antinuclear antibodies (significance uncertain) –21.8%

• **RED CELL AUTOANTIBODIES** – 1.9%

In a survey of 603 UK general vets, within the previous 12 months, the following side effects were observed by the percentage of vets shown (Higgs et al, 2014):

Vomiting 69%, anorexia 47%, facial pruritus 44.8%, azotaemia 22.7%, **ANAEMIA** 11.8%, **LEUKOPAENIA** 10.9%, **HEPATIC DAMAGE** 9.6%, **NEUTROPAENIA** 8.4%, thrombocytopaenia 8.4%, lymphadenopathy 4.7%, sudden death 0.9%

General awareness of the prevalence of these adverse events would be enhanced by improved participation within the VMD pharmacovigilance scheme. The GPs reported adverse events at the following frequencies:

Never reported adverse event (49.6%); reported up to 25% of adverse events (36.5%); reported 26% to 99% (8%); reported 100% (5.9%).

In addition, prolonged use of methimazole for four years or more has been associated with an increase in carcinoma prevalence from three per cent to 20 per cent (Peterson and Broome, 2012), and although unlikely to be a direct effect of methimazole, this is not a desired outcome. Further studies are needed to monitor the outcome with other long-term management, such as iodine-depleted diets.

Key: Red = discontinue methimazole permanently; **BOLD CAPITALS** = life threatening; Blue = monitor

BOLD CAPITALS = may become life threatening;

Green = try lower dose and continue if tolerated

Panel 3. Client and vet concerns in selecting radioiodine, and a long-term treatment plan, respectively

Client concerns ranked from 1 (least) to 10 (most; Boland et al, 2014).

Hospitalisation period – 7; side effects to the cat following RIT – 3; travel to radioiodine centre – 2; health risks themselves – 1; waiting period for referral – 1; cost of radioiodine – 1

Percentage of UK GP vets reporting the stated concern as “important” and “very important” when devising long-term treatment plans (Higgs et al, 2014).

Owner compliance with medication – 98%; ease of drug administration – 97.7%; co-morbid disease – 96.5%; cost of treatment – 80.9%; cost of monitoring – 78.6%; risk of surgical complications – 76.3%; age – 66.7%; risk of drug side effects – 65.3%; ease of referral for RIT – 48.1%; whether cat is insured – 30.5%; indoor versus outdoor cat – 19.7%

Panel 4. Outcome data for 524 hyperthyroid cats treated with radioiodine (Peterson and Becker, 1995)

• 84.7% become euthyroid within 25 days (mean 9.5 days).

• 13.8% are delayed responders remaining initially hyperthyroid, but euthyroid by six months.

• 1.5% remain hyperthyroid at six months. Most respond to a second treatment; carcinoma is suspected if still unresponsive. Radioiodine is the treatment of choice for carcinoma, but at a high dose.

• 2.1% required supplementation with T**4** if clinically hypothyroid (excessive weight gain, matted coat, personality changes, for example, can become subdued/withdrawn), or if concurrent azotaemia. NOTE: life expectancy is reduced by half when azotaemia and hypothyroidism are concurrent (Williams et al, 2010).

• Of those cured, approximately 2.5% show future de novo hyperthyroidism (mean 3.4 years).

Summary: a 94.2% cure rate, occasional T_4 supplementation required, occasional non-responders.

Figure 1. The period of separation during RIT is the biggest concern for prospective clients. Environmental enrichment is important to both clients and cats.

IMAGE: The Hyperthyroid Cat Centre.