CRITICALLY APPRAISED TOPIC:

Comparison of the clinical efficacy of radioiodine, oral methimazole and transdermal methimazole in the treatment of feline hyperthyroidism

Radioiodine, oral methimazole and transdermal methimazole are all effective in the treatment of feline hyperthyroidism.

BY PATRICK SHEARER, BVMS, PHD
CONTRIBUTING AUTHOR

CLINICAL QUESTION

In cats newly diagnosed with hyperthyroidism, do radioiodine, oral methimazole and transdermal methimazole have similar clinical efficacy?

CLINICAL BOTTOM LINE

Radioiodine, oral methimazole and transdermal methimazole are all effective treatment options for feline hyperthyroidism. Determination of the most effective therapy, however, is not possible due to a lack of published controlled trials comparing efficacy between agents. Studies evaluating individual treatments are not directly comparable due to different research methods. Client and patient factors (e.g., cooperation, compliance and follow-up), combination protocols (e.g., pre-treatment with methimazole before radioiodine administration), differences in side effects and cost make clinical judgment and communication the key factors in choosing and monitoring treatment for this disease.

EVIDENCE SUMMARY

PubMed database search details (inception through current):

- Feline hyperthyroidism (veterinary subset):
  - (“felidae”[MeSH Terms] OR “felidae”[All Fields] OR “feline”[All Fields]) AND (“hyperthyroidism”[MeSH Terms] OR “hyperthyroidism”[All Fields])

MAIN RESULTS

- One randomized controlled trial has compared oral and transdermal methimazole. Oral methimazole was more effective after two weeks of therapy, but by four weeks the difference was not statistically significant.3

- There is a limited amount of moderate-quality research on each individual agent. These studies show that oral methimazole, transdermal methimazole and radioiodine can all be effective treatments for feline hyperthyroidism.2-9

- Radioiodine was found to be an effective treatment; however, some studies included cats that had been pre-treated with methimazole. Thus, a comparison of efficacy between radioiodine and either oral or transdermal methimazole is not possible.2,5,6,9

- The nature and severity of side effects, longevity of results and ease of administration vary greatly between treatments.10-15
**Figure 1: Strength of Evidence**

- **Systematic Reviews/Critically Appraised Topics**
  - Sartor, et al. (2004); Theon, et al. (1994)
- **Randomized Controlled Trials**
  - Slater, et al. (1994)
- **Cohort Studies**
- **Case-Control Studies**
- **Case Series, Case Reports**
  - Frénais, et al. (2009); van Dijl and Hof (2009); Lécuyer, et al. (2006); Hoffmann, et al. (2003); Peteron, et al. (1995); Meric, et al. (1986)
- **Background Information, Experimental Research Models, Expert Opinions**
  - Trepanier (2006); Behrend, (2006); Peterson (2006); Lass and Kaniuka (2005); Kintzer (1994)

*See corresponding Evidence Summary, Table 1, pages 6-8.

**COMMENTS**

- For each individual patient, selection of an appropriate therapy depends on balancing ease of administration, owner and patient compliance, potential for side effects, nature of side effects and cost.
- For example, a single treatment with radiiodine is likely to be effective. However, there is a small risk of hypothyroidism and treatment requires access to specialized facilities and, hence, may be expensive. Conversely, treatment with methimazole is lifelong, requires excellent patient cooperation and owner compliance and is associated with more side effects than radiiodine.

**CAT Appraiser:** Patrick Shearer, BVMS, PhD
**Date CAT was “born”/expiration date:** 12/08/2010

**References**

Table 1: Evidence Summary

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Participants (n)</th>
<th>Study Design &amp; Measures</th>
<th>Intervention</th>
<th>Findings/Conclusions</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Frénais R, Rosenberg O, Burgaud S, et al. (2009)</td>
<td>Forty-four client-owned cats with history and clinical signs consistent with hyperthyroidism</td>
<td>Multicenter, self-controlled case series. Cats had a history and clinical signs consistent with hyperthyroidism and total T4 &gt; 50 nmol/L. Primary measures were total T4 concentration and clinical assessment (hypo-, eu- or hyperthyroid). Clinicians were blinded to total T4 measurements when making clinical assessments.</td>
<td>Treatment was started at 15 mg carbimazole once daily; clinical response was assessed after 10 days, and 3,5,8, 26 and 53 weeks and dose adjusted as required.</td>
<td>Twenty cats completed the study period. The median maintenance dose of carbimazole was 10 mg (range 10 to 15 mg) and 15 mg (5 to 25 mg) once daily after 3 and 53 weeks, respectively. Median total thyroxine concentration dropped significantly from 118 nmol/L (50 to 320 nmol/L) at presentation to 33 nmol/L (n=40) after 10 days, 31 nmol/L (n=34) at 3 weeks and 21 nmol/L (n=18) at 53 weeks. Clinical signs improved or resolved in almost all cats within 3 weeks after starting treatment.</td>
<td>Limited follow-up on some cases, leading to a small sample size</td>
</tr>
<tr>
<td>van Dijl IC, Hof AJ (2009)</td>
<td>Eighty-three cats, diagnosed as hyperthyroid by referring veterinarians (based on clinical signs and total T4)</td>
<td>Self-controlled case series. Blood samples for measurement of plasma concentrations of total thyroxine (total T4), urea, and creatinine were collected prior to, 10 days after and several months after treatment. In addition, arterial blood pressure was measured before and 10 days after treatment.</td>
<td>Cats treated with 131I at between 4-6 mCi</td>
<td>Ten days and several months after 131I treatment, plasma total T4 concentrations had decreased below the upper limit of the reference range in 64 (77%) and 72 cats (87%), respectively. In four cats, the plasma total T4 concentration had decreased below the lower limit of the reference range, but only two cats had symptoms of hypothyroidism.</td>
<td>Study identified or described incorrectly. Sixty-five cats (78%) had been pre-treated with antithyroid drugs, with a washout period of only 3 days before 131I. Analysis did not account for the effect of pre-treatment antithyroid drugs. Blood samples analyzed by different labs with different reference ranges.</td>
</tr>
<tr>
<td>Trepynier (2006)</td>
<td>n/a</td>
<td>Review</td>
<td>Oral methimazole, oral carbimazole, transdermal methimazole, effective in treatment of hyperthyroidism. Radioidoine is preferred, because it has fewer side effects and is curative, although methimazole is better tolerated in cats with renal disease and treatment may be easier to arrange.</td>
<td>n/a</td>
<td></td>
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<tr>
<td>Behrend (2006)</td>
<td>n/a</td>
<td>Review</td>
<td>Oral and transdermal methimazole effective in treatment of hyperthyroidism.</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Lécuyer M, Prin S, Dunn ME, et al. (2006)</td>
<td>Thirteen client-owned cats newly diagnosed with hyperthyroidism</td>
<td>Self-controlled case series. Baseline hematologic and biochemical values, along with serum thyroxine (total T4) levels, were obtained on presentation (day 0). Cats were evaluated at 14 d (D14) and 28 d (D28) following transdermal therapy. At each visit, a physical examination, a complete blood cell count, a serum biochemical analysis, and a serum total T4 evaluation were performed.</td>
<td>5 mg (0.1 ml) (concentration of 50 mg/ml) applied to the internal ear pinna every 12 h for 28 d.</td>
<td>Ten cats completed the study. Clinical improvement, as well as a significant decrease in total T4, was noted in all cats. Serum total T4 measured at D14 and D28 were significantly lower at 27.44 nmol/L, s = 37.51 and 14.63 nmol/L, s = 10.65, respectively (P = 0.0001), as compared with values at D0 (97.31 nmol/L, s = 37.55).</td>
<td>Small sample size</td>
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### Table 1: Evidence Summary (cont’d)

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<tr>
<td>Peterson ME (2006)</td>
<td>n/a</td>
<td>Review</td>
<td>Ho cloiodine effective</td>
<td></td>
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<tr>
<td>Lass P, Kaniuka S (2005)</td>
<td>n/a</td>
<td>Review</td>
<td>Radioiodine is effective treatment</td>
<td>Obscure journal</td>
<td></td>
</tr>
<tr>
<td>Sartor LL, Trespanier LA, Kroll MM, et al. (2004)</td>
<td>Forty-seven client-owned cats newly diagnosed with hyperthyroidism</td>
<td>Randomized controlled trial. Cats were evaluated at weeks 0, 2, and 4 with a physical exam, body weight determination, CBC, biochemical panel, urinalysis, measurement of total levothyroxine (total T4) concentration, indirect Doppler blood pressure determination, and completion of an owner questionnaire. Data between the two groups and over time were compared by nonparametric methods.</td>
<td>Cats received either transdermal methimazole in pluriomic lctihin organel (PLO) applied to the inner pinna, or oral methimazole (2.5 mg 12 h for either route).</td>
<td>Forty-four cats followed the protocol (17 oral and 27 transdermal). Significantly more cats treated with oral methimazole had serum total T4 concentrations within the reference range after 2 weeks (14 of 16 cats) compared to those treated by the transdermal route (14 of 25; P 0.027). This difference was no longer significant by 4 weeks of treatment (9 of 11 for oral versus 14 of 23 for transdermal), possibly because of inadequate numbers evaluated by four weeks. Cats treated with oral methimazole had a higher incidence of gastrointestinal (GI) adverse effects (four of 17 cats) compared to the cats treated with transdermal methimazole (1 of 27; P 0.04), but no differences were found between groups in the incidence of neutropenia, hepatotoxicity or facial excoriation.</td>
<td>Low numbers of participants in the 4-week follow-up group</td>
</tr>
<tr>
<td>Hoffmann G, Marks SL, Taboada I, et al. (2003)</td>
<td>Thirteen client-owned cats, identified from records of an endocrine diagnostic laboratory</td>
<td>Self-controlled case series. During the treatment period, cats were re-evaluated at a mean of 4.3 weeks (recheck-1), and again at a mean of 5.4 months (recheck-2).</td>
<td>Methimazole was formulated in a PLO-based vehicle and was applied to the inner pinna of the ear at a dosage ranging from 2.5 mg/cat q 24 h to 10 mg/cat q 12 h.</td>
<td>Clinical improvement was observed, and significant decreases in thyroxine concentrations were measured at recheck-1 (mean 39.57 nmol/L; SEM: 14.4, SD: 41.2) and recheck-2 (mean: 36.71 nmol/L; SEM: 13.9, SD: 45.56) compared to pretreatment concentrations (mean: 97.5 nmol/L; SEM: 11.42; SD: 39.9). No adverse effects were reported.</td>
<td>Inconsistent follow-up times, low numbers of patients at follow-up visits. Two patients were pre-treated with oral methimazole</td>
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<tr>
<td>Peterson ME, Becker DV (1995)</td>
<td>524 client-owned cats diagnosed with hyperthyroidism at the Animal Medical Center and treated with radioiodine at Cornell University Medical College.</td>
<td>Self-controlled case series. Cats administered methimazole had the treatment stopped 1-2 weeks before radioiodine. Fourteen cats had partial surgical thyroid ablation. Cats were divided into three groups based on a score given according to clinical signs, size of thyroid gland and magnitude of total T4 concentration. Total T4 was measured on the day of discharge, 2 to 3 months post-discharge and 6 to 12 months post-discharge, then once per year thereafter.</td>
<td>Cats with low, moderate or high scores were treated with either 2-3.4 mCi, 3.5-4.4 mCi or 4.5-6 mCi, respectively.</td>
<td>When discharged from the hospital, 80 cats (15.3%) still had high total T4 concentrations but by 6 months post-treatment only eight cats (1.5%) were persistently hyperthyroid. Eleven cats (2.1%) developed clinical and clinicopathologic signs consistent with hyperthyroidism and required thyroxine supplementation.</td>
<td>Materials and methods didn’t mention a blocking design, statistical analysis doesn’t account for the design.</td>
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**Radioiodine is effective treatment in treating hyperthyroidism.**

The use of radioiodine has been shown to be effective in treating hyperthyroidism, as evidenced by the significant decreases in thyroxine concentrations measured at recheck-1 and recheck-2 in the study by Hoffmann et al. (2003). However, the study also highlights the limitations of radioiodine treatment, including inconsistent follow-up times and low numbers of patients at follow-up visits. Additionally, the study notes the potential for adverse effects, such as gastrointestinal (GI) adverse effects and clinical signs, which were observed in some cats treated with oral methimazole.

**Other interventions are also effective.**

Interventions such as surgical thyroid ablation and the use of methimazole (administered orally or transdermally) have also been shown to be effective in treating hyperthyroidism. For example, Sartor et al. (2004) found that cats treated with transdermal methimazole had lower total T4 concentrations compared to those treated with oral methimazole, although no differences were found in the incidence of neutropenia, hepatotoxicity or facial excoriation.

**The choice of treatment should be based on individual patient needs.**

The choice of treatment for hyperthyroidism should be based on individual patient needs, taking into account factors such as the severity of clinical signs, the presence of adverse effects, and the feasibility of different treatment options. For example, patients with moderate to high scores of hyperthyroidism may require more aggressive treatment options, such as radioiodine, while patients with low scores may be better suited for less invasive treatments, such as methimazole or surgical thyroid ablation.
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<tr>
<td>Théon AP, Van Vechten MK, Feldman E (1994)</td>
<td>120 client-owned cats with confirmed hyperthyroidism</td>
<td>Randomized controlled trial. Total T4 measured at 1, 3 and 6 months post-treatment.</td>
<td>Cats received a dose of radioiodine by either IV or SC administration that delivered 150 μg to the thyroid.</td>
<td>85% of cats treated IV and 84% treated SC were euthyroid 4 years after treatment. SC administration is as effective as IV, safer to personnel and less stressful to cats.</td>
<td></td>
</tr>
<tr>
<td>Kintzer P (1994)</td>
<td>n/a</td>
<td>Review</td>
<td>Oral methimazole and radioiodine effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slater M, Komkov A, Robinson LE, et al. (1994)</td>
<td>255 client-owned cats referred to the Texas A&amp;M Veterinary Teaching Hospital between January 1985 and December 1990</td>
<td>Retrospective study using data from a referral institute plus follow-up telephone consultations with veterinarians and owners. Outcome was defined as either: 1) asymptomatic, 2) continued hyperthyroid or 3) hypothyroid. Standard questions were asked about outcome, diseases ongoing or diagnosed at the time of hyperthyroidism diagnosis and survival.</td>
<td>The dose of radioactive iodine administered was estimated by taking into consideration the size and number of the thyroid nodules and the total body weight of the cat. For example, a 4.5 kg cat with three large nodules would get a higher dose (e.g., 222 MBq or 6 μCi) but a 3 kg cat with a single nodule would receive 111 to 148 MBq (3 to 4 μCi). Median dose of L-T4 1.0 mg/kg: 18.1 ± 3.9 MBq (4.9 μCi) (range 13.6 ± 29.3 MBq (2.8 ± 8.9 μCi)).</td>
<td>Cats with hyperthyroidism were significantly older than the control population (P ≤ 0.001). Among cats 7 years and older, there was no significant breed predisposition to hyperthyroidism. When neuter status was used in the gender analysis, there was a significant association between gender and hyperthyroidism. However, when all females combined and all males combined were compared, no association with hyperthyroidism was found (P = 0.45). Eighty-five percent (200/236) of treated cats became euthyroid after treatment. Four percent (10/236) were hyperthyroid and 9% (22/236) were hypothyroid at the conclusion of the study. Age at diagnosis, total dose of L-T4, duration of treatment, peak radiation level and median time that methimazole treatment was discontinued prior to radioactive iodine therapy.</td>
<td>A single multivariate analysis may have been more suitable than multiple bivariate analyses</td>
</tr>
<tr>
<td>Meric SM, Hawkins EC, Washabau RJ, et al. (1986)</td>
<td>Thirteen client-owned cats referred to the UC Davis Veterinary Medical Teaching Hospital</td>
<td>Self-controlled case series. Total T4 measured before treatment, at 12 h intervals after treatment in 10 cats and 8 h intervals in 21 cats. Also measured one month after therapy in 29 cats.</td>
<td>1.5 to 6.13 μCi, resulting in a dose of 20,000 rads to the thyroid.</td>
<td>Total T4 concentrations before administration were 5.3 to 51 μg/dL with a median of 11 μg/dL. 16 cats (55%) were euthyroid by day 4 after administration and 23 (74%) by day 8. Of the 29 cats evaluated 1 month after treatment, all were clinically improved and 24 (83%) were euthyroid. Three cats (10%) remained hyperthyroid and 2 (7%) were hypothyroid.</td>
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