

Medical Management of Hyperthyroidism

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Radioiodine is considered the treatment of choice for hyperthyroidism, but in some situations, methimazole therapy is preferred, such as in cats with pre-existing renal insufficiency. Methimazole blocks thyroid hormone synthesis, and controls hyperthyroidism in more than 90% of cats that tolerate the drug. Unfavorable outcomes are usually due to side effects such as gastrointestinal (GI) upset, facial excoriation, thrombocytopenia, neutropenia, or liver enzyme elevations; warfarin-like coagulopathy or myasthenia gravis have been reported but are rare. Because restoration of euthyroidism can lead to a drop in glomerular filtration rate, all cats treated with methimazole should be monitored with BUN and creatinine, in addition to serum T4, complete blood count, and liver enzymes. Transdermal methimazole is associated with fewer GI side effects, and can be used in cats with simple vomiting or inappetence from oral methimazole. Hypertension may not resolve immediately when serum T4 is normalized, and moderate to severe hypertension should be treated concurrently with atenolol, amlodipine, or an ACE inhibitor. Alternatives to methimazole include carbimazole, propylthiouracil, or iodinated contrast agents.

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Hyperthyroidism is the most common endocrine disorder in cats, with a 2% prevalence in cats presenting to teaching hospitals.¹ Management options include radioiodine therapy, thyroidectomy, or medical treatment with antithyroid drugs such as methimazole. Radioiodine is considered the treatment of choice for hyperthyroidism, based on its high efficacy and relative lack of complications (Table 1). However, there are some situations in which methimazole therapy may be preferred over radioiodine. Practical considerations, such as lack of a convenient referral center with a radiation license, client fears about radiation or quarantine, or initial cost to the client, may drive the use of methimazole. Methimazole can be used before thyroidectomy to normalize serum thyroxine (T4) concentrations,² and reduce the risk of complications, such as tachyarrhythmias, during anesthesia. Methimazole, which is reversible, is also useful in cats with renal insufficiency, either for long term therapy or as a “test dose” to determine whether serum T4 can be safely lowered without causing renal decompensation.

Methimazole Actions, Dosing, and Efficacy

Methimazole blocks thyroid hormone synthesis by inhibiting thyroid peroxidase, an enzyme involved in the oxidation of iodide to iodine, incorporation of iodine into thyroglobulin, and coupling of tyrosine residues to form T4 and triiodothyronine (T3). Methimazole does not block the release of preformed thyroid hormone, which explains the delay of 2 to 4 weeks before serum T4 concentrations fully normalize after beginning treatment in cats.² Methimazole does not decrease goiter size, and in fact goiters may become larger over time despite therapy.

Typical starting doses of methimazole range from 1.25 to 2.5 mg twice daily (Table 2). More frequent dosing (q. 8 hours) is rarely necessary. Higher doses of 5 mg 2 to 3 times daily, used in original cases of cats with relatively high serum T4 concentrations,² are probably not needed for initial therapy of cats with mild to moderate hyperthyroidism, and could potentially increase the risk of renal decompensation from a rapid fall in serum T4. Methimazole is effective in normalizing T4 in the majority of treated cats, and this effect is dose-dependent.² Starting dosages can be titrated upwards if there is an inadequate initial response to lower doses of methimazole over 2 to 4 weeks. In cats that tolerate methimazole without side effects, efficacy is greater than 90%.²⁻⁴

In humans, methimazole has a long residence time in the thyroid gland, and can exert antithyroid effects for 24 hours

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Table 1 Advantages and Disadvantages of Major Therapies for Feline Hyperthyroidism

Treatment	Advantages	Disadvantages
Radioiodine	>90% efficacy ^{36,60} Single injection Few side effects (rare dysphagia) ³⁶ Curative	High initial expense Somewhat limited availability Irreversible
Thyroidectomy	~90% efficacy ⁶¹ Curative	High initial expense Anesthetic risks Risk of hypoparathyroidism Risk of recurrent laryngeal nerve damage Irreversible
Methimazole	Low initial expense ~90% efficacy in cats that do not have side effects Reversible	Daily drug administration Drug side effects

or more,^{5,6} despite a short plasma elimination half life. Because of this, methimazole can be given once daily in humans with remission rates that are comparable to divided daily dosing.^{7,8} In our study of 40 hyperthyroid cats, we found that once daily dosing (5 mg q. 24 hour) was less effective than divided dosing (2.5 mg q. 12 hour), with only 54% of cats euthyroid after 2 weeks of once daily treatment, compared with 87% of cats treated with divided dosing.⁴ Therefore, unless clients are absolutely unable to dose more frequently than once daily, divided twice daily dosing of methimazole is preferred to maximize efficacy. Dosing less frequently than once daily is unlikely to be effective, as serum T4 concentrations rise to pretreatment hyperthyroid values within 48 hours after discontinuing methimazole.²

Methimazole Side Effects

Side effects of methimazole have been reported in 18% of treated cats, to include blood dyscrasias, facial excoriation, hepatotoxicity, and simple gastrointestinal (GI) upset.² Positive antinuclear antibodies (ANA) have been documented in over 20% of treated cats, with uncertain clinical significance.² The risk of positive ANA increases with dose and duration of therapy, and can be reversed with dose reduction. Positive ANA were not associated with blood dyscrasias or other adverse clinical events, and no affected cats had lupus-like signs.² The cats reported in this large series had relatively high serum T4 concentrations (with many cats >20 µg/dL) and were administered 10 to 15 mg of methimazole per day. The incidence of positive ANA has not been subsequently evaluated in a comparably large group of cats with milder hyperthyroidism treated with lower daily doses of methimazole.

Blood Dyscrasias

Methimazole can lead to neutropenia and/or thrombocytopenia in 3 to 9% of treated cats.^{2,3} Cats with methimazole-induced blood dyscrasias usually recover within a week of drug discontinuation. Continuing methimazole in the face of thrombocytopenia has lead to clinically significant hemorrhage, including epistaxis and oral bleeding.² Rechallenge with methimazole in one cat with neutropenia lead to a recurrence of severe neutropenia within seven days of re-administration.²

Although the mechanisms for these blood dyscrasias in cats have not been established, methimazole-induced neutropenia in humans is associated with an arrest of myeloid progenitors in the bone marrow.^{9,10} Serum from affected humans inhibits normal granulocyte-macrophage CFUs in vitro, suggesting antibody or cytokine-mediated effects.¹¹ Studies in humans have found an association between methimazole-associated neutropenia and the presence of antineutrophil antibodies and certain human leukocyte antigen (HLA) gene mutations, further implicating autoimmune mechanisms.^{12,13} Treatment with granulocyte-macrophage colony stimulating factor (GM-CSF) has been advocated in humans,¹⁴ but does not appear to hasten recovery in most cases.¹⁵ In cats, methimazole treatment has been associated with red cell autoantibodies,² but the presence of antibodies to platelet or neutrophil antigens has not been evaluated.

Facial Excoriation

Approximately 2 to 3% of cats treated with methimazole will develop excoriations of the face and neck,² leading to characteristic scabbed lesions in front of the pinnae. Generalized erythema and pruritus may also occur. These excoriations are only partially responsive to glucocorticoids, and drug discontinuation is almost always required.² Pruritis has also been reported in human patients treated with methimazole, but the mechanisms for these reactions have not been explored.¹⁴

Hepatotoxicity

Methimazole is associated rarely with cholestatic hepatopathy in humans.¹⁶ Increases in serum alkaline phosphatase (SAP) and bilirubin, or alanine aminotransferase (ALT), are observed in approximately 2% of cats treated with methimazole^{2,3}; liver biopsy in one cat showed hepatic necrosis and degeneration.² Liver enzyme elevations are usually reversible over several weeks following drug discontinuation, although nutritional and fluid support may be required. Rechallenge in one cat lead to recurrent hepatopathy,² and future drug avoidance is generally recommended. In rodent models of methimazole hepatotoxicity, an oxidative metabolite has been implicated, and toxicity is exacerbated by glutathione depletion.¹⁷ The role of glutathione depletion, or supplementation, in methimazole-associated hepatotoxicity in cats has not been evaluated.

Simple Gastrointestinal Upset

Anorexia, vomiting, and lethargy are reported in approximately 10% of cats treated with methimazole at 10 to 15 mg per day.² Simple gastrointestinal (GI) upset is most common in the first 2 to 4 weeks of treatment, and can resolve with a

Table 2 Drugs Useful in the Medical Management of Hyperthyroidism

Drug	Indications	Dosage	Side effects	Comments
Methimazole	Hyperthyroid cats with azotemia, or for clients declining radioiodine	1.25 to 5 mg per cat twice daily (start at lower end)	GI upset Facial excoriation Blood dyscrasias Hepatopathy	Transdermal route has fewer GI side effects
Carbimazole	Prodrug of methimazole	2.5 to 5 mg per cat twice daily	GI upset Facial excoriation Blood dyscrasias Hepatopathy	
Iopanoic acid or calcium ipodate	Adjunct control of T3 in cats intolerant of methimazole	100 to 200 mg per day (empirical)		Inhibits conversion of T4 to T3 Effects may be transient
Propylthiouracil	Unclear if useful for cats intolerant of methimazole	25 mg per cat twice daily (empirical)	Hemolytic anemia Thrombocytopenia Bleeding diathesis	
Propranolol	Control of tachyarrhythmias or hyperactivity; adjunct control of T3 in cats intolerant of full dosages of methimazole	2.5 to 5 mg per cat three times daily	Bronchoconstriction in cats with prior lower airway disease	Inhibits conversion of T4 to T3
Atenolol	Control of tachyarrhythmias or hyperactivity	3.125 to 6.25 mg per cat twice daily		Beta-one selective blocker
Enalapril or benazepril	Control of hypertension	0.5 mg/kg once daily	Lethargy, inappetence	Potential effect of limiting glomerulosclerosis in cats with renal disease; benazepril does not accumulate in renal failure
Amlodipine	Control of moderate to severe hypertension	0.625 mg per cat once daily	Lethargy, inappetence	Drug of choice for severe hypertension

reduction in drug dosage. These signs may be due in part to direct gastric irritation from the drug, because transdermal administration of methimazole is associated with significantly fewer GI side effects than the oral route.³

Renal Decompensation

Cats with hyperthyroidism have abnormally high glomerular filtration rates (GFR), as measured by iothexol clearance or renal scintigraphy.¹⁸⁻²⁰ Treating hyperthyroidism with methimazole leads to decreases in GFR in most hyperthyroid cats.¹⁸ Similar results have been found in hyperthyroid cats treated with thyroidectomy or radioiodine,²¹ with 15 to 22% of cats developing new azotemia.^{19,20} While these biochemical changes are generally clinically silent, occasional cats will develop signs of illness referable to underlying renal disease.¹⁸ Because methimazole is reversible, it is the preferred approach for initial treatment of hyperthyroid cats with pre-existing azotemia, to determine whether lowering of serum T4 will lead to unacceptable renal decompensation.²¹

Coagulation Abnormalities

In humans, methimazole is uncommonly associated with hypoprothrombinemia.²² Methimazole, and to a lesser extent propylthiouracil, inhibit vitamin K-dependent clotting factor activation (γ -carboxylation) and epoxide reductase (necessary for vitamin K recycling, and the same enzyme targeted

by warfarin), at high concentrations.²² In a study of 20 hyperthyroid cats treated with methimazole, there were no significant changes in prothrombin time or activated partial thromboplastin time, but one cat developed a prolonged PIVKA clotting time.²³ No cats had clinically significant bleeding. This suggests a possible, but apparently uncommon, "warfarin-like" effect of methimazole in cats as well. This may explain why a single methimazole-treated cat (0.3%) in the large case series² developed a bleeding diathesis without thrombocytopenia. This reaction is rare enough not to warrant routine monitoring, but should be considered in any cat presenting with hemorrhage that is also being treated with methimazole.

Acquired Myasthenia Gravis

Another apparently rare side effect of methimazole in cats is the development of acquired myasthenia gravis.²⁴ Neuromuscular weakness, along with positive antibody titers to the acetylcholine receptor, were reported in 4 cats treated with methimazole for 2 to 4 months. Creatinine kinase was elevated in 2 cats, and 1 cat had a biopsy diagnosis of concurrent polymyositis. Cats responded to drug discontinuation, or the addition of prednisone to the methimazole treatment regimen. One cat relapsed with re-introduction of the drug. Although this does not appear to be a side effect of methimazole

in humans, hyperthyroidism itself can copresent with myasthenia in humans²⁵; in 1 human patient, methimazole therapy was thought to worsen the clinical signs of myasthenia.²⁶

Clinical Monitoring

Based on the spectrum of possible adverse reactions to methimazole, clinical monitoring at 2 to 3 and 4 to 6 weeks of treatment should include a complete blood count (CBC), ALT and SAP, and blood urea nitrogen (BUN) and creatinine, in addition to serum T4. This same work-up should also be performed if a cat becomes clinically ill during methimazole treatment, since it is important to differentiate simple GI upset (for which a lower dose or a switch to transdermal methimazole may be curative) from blood dyscrasias or hepatopathy, for which methimazole should be discontinued.

It is also important to measure renal function and T4 simultaneously during methimazole therapy, to determine whether the cat's kidneys can tolerate the level of GFR associated with normal thyroid function. If a cat becomes newly azotemic, with clinical signs of polyuria, polydipsia, and inappetence, the dosage of methimazole can be titrated to maintain the serum T4 in the high normal range, with additional use of drugs to control hypertension and tachyarrhythmias (see Management of Hypertension, below).

Transdermal Methimazole

Methimazole is available through custom compounding pharmacies in a transdermal formulation in pluronic lecithin organogel (PLO). PLO acts as a permeation enhancer to allow drug absorption across the stratum corneum. Although methimazole in PLO has been shown to have poor absorption in cats after a single dose,²⁷ chronic dosing in hyperthyroid cats is effective in lowering serum T4 concentrations.^{3,28} Methimazole in PLO is applied to the cat's inner pinna, alternating ears with each dose. Owners wear examination gloves or finger cots during administration, and are instructed to remove crusted material with a moistened cotton ball before the next dose.

In a randomized trial comparing oral to transdermal methimazole in PLO in 47 hyperthyroid cats (2.5 mg q. 12 hour), transdermal methimazole had significantly fewer gastrointestinal side effects (4% of cats) compared with oral (24% of cats).³ There were no differences in the incidence of facial excoriation, neutropenia, thrombocytopenia, or hepatotoxicity between routes. However, transdermal methimazole was associated with somewhat lower efficacy (only 67% euthyroid by 4 weeks) compared with oral methimazole (82% euthyroid by 4 weeks). This may be because of lower bioavailability of the transdermal formulation.

Drawbacks of methimazole in PLO include erythema at the dosing site in some cats, increased formulation costs, and unproven drug stability beyond 2 weeks. However, methimazole in PLO appears to be effective (anecdotally) beyond 2 weeks. We recommend that serum T4 values be checked toward the end of a 2-month prescription of the transdermal formulation, to confirm that thyroid control persists.

Lack of Response to Methimazole

The most common reason for failure of methimazole therapy is the development of side effects requiring drug discontinuation. It is otherwise uncommon for cats to fail to respond to a dose titration of methimazole; in one series of 262 cats (some severely hyperthyroid), less than 1% of cats were refractory to titrated dosages of methimazole.² However, some cats will not tolerate the dose of methimazole that is needed to normalize serum T4 concentrations. In these cases, radioiodine is indicated. For cats that are not good candidates for radioiodine (eg, moderate to severe azotemia, advanced age with other debilitating problems), an alternative approach is to use lower doses of methimazole that are tolerated, and add a beta blocker (eg, atenolol, 3.125 or 6.25 mg per cat twice daily) to control tachycardia. These cats need to be monitored for changes in renal function or for continued weight loss.

Methimazole Before Pertechnetate Scanning or Radioiodine Therapy

Because methimazole does not inhibit iodide uptake by the thyroid, concurrent methimazole therapy does inhibit ^{99m}Tc-pertechnetate thyroid scanning in hyperthyroid cats,²⁹ and in fact, may enhance imaging.³⁰ Methimazole does inhibit organification of iodine, which would be expected to decrease the residence time of radioiodine within the thyroid. In humans, patients randomized to treatment with methimazole up to 4 days before radioiodine had no difference in outcome when compared with patients given no methimazole pretreatment.³¹ However, other studies in humans have found that administration of methimazole before³² or immediately after³³ radioiodine was associated with poorer responses. Retrospective studies in hyperthyroid cats have found no association between the time of methimazole discontinuation before radioiodine, and long-term radioiodine efficacy.^{34,35} Even cats that had methimazole discontinued less than 5 days before radioiodine had no overall difference in outcome compared with cats with a longer washout period.³⁵ However, there is no data to support the continuation of methimazole up until the time of radioiodine therapy. A 1- to 2-week washout period for methimazole has been adopted by many radioiodine facilities, based on efficacy data from the largest cases series published (524 cats).³⁶ There is some evidence to suggest that recent methimazole discontinuation may actually have a short term rebound effect to enhance radioiodine efficacy.³⁷ This is consistent with a study in normal cats, in which methimazole, when discontinued 4 to 9 days before radioiodine, lead to maximally increased radioiodine (¹²³I) uptake compared with no methimazole treatment.³⁰

Management of Hypertension

Hypertension has been reported to be as prevalent as 87% in hyperthyroid cats³⁸; however, it is possible that hospital-induced stress affected the readings in this early study. Subse-

quent surveys of cats with hyperthyroidism report the prevalence of hypertension in hyperthyroid cats to be 5 to 22%,^{3,4,39} with many cats with hypertension having concurrent azotemia.³⁹

Normalizing serum T4 may not significantly control blood pressure in the first weeks of therapy.⁴ Therefore, direct management of moderate to severe hypertension is indicated along with antithyroid treatment. Commonly used antihypertensive agents include amlodipine, beta-blockers, or the angiotensin-converting enzyme (ACE) inhibitors enalapril or benazepril. There have been no clinical trials evaluating the comparative efficacy of these drugs in this setting. Beta blockers such as atenolol may be particularly useful if signs of hyperactivity or tachyarrhythmias are present. The calcium channel blocker amlodipine (starting dose, 0.625 mg per cat once daily⁴⁰;) may be particularly effective for severe hypertension.⁴¹ ACE inhibitors such as benazepril (0.5 mg/kg once daily) have the potential benefit of reducing intraglomerular pressure in patients with renal disease.⁴² In cats with overt azotemia, benazepril, which does not accumulate in renal insufficiency,⁴³ has an advantage over enalapril.

In some hyperthyroid cats without initial hypertension, hypertension can actually develop several months after treatment for hyperthyroidism,³⁹ possibly because of unmasking of underlying renal insufficiency. Therefore, rechecking cats for hypertension 2 to 3 months after restoration of a euthyroid state is indicated.

Other Antithyroid Drug Options

Propylthiouracil (PTU)

Propylthiouracil (PTU) was the first drug used in the management of hyperthyroid cats in the early 1980s.⁴⁴ This drug is less potent than methimazole, and required high doses (eg, 50 mg q. 8 to 12 hours) to normalize serum T4 concentrations. PTU was associated with an unacceptably high incidence of adverse events, to include positive ANA, Coombs positive hemolytic anemia, and thrombocytopenia with bleeding diathesis, in approximately 8% of hyperthyroid cats.⁴⁵ This syndrome was reproduced experimentally in more than 50% of cats in a research setting,⁴⁶ with a dose-dependent induction of ANA that was attributed to a reactive sulfur atom in the drug's structure.⁴⁷ A similar atom is also present in methimazole, and, unfortunately, is necessary for the antithyroid action of these drugs.⁴⁸ Later attempts to experimentally recreate this syndrome in cats were not successful. Researchers hypothesized that taurine deficiency (with associated impaired drug elimination) may have exacerbated the side effects of PTU when it was first used.⁴⁹ Methimazole and PTU share structural similarities, and patients with blood dyscrasias, hepatopathy, or facial excoriation from methimazole may well have similar adverse reactions to PTU; however, the degree of cross-reactivity has not been critically examined in cats.

Carbimazole

Carbimazole is a substituted derivative of methimazole that was developed with expectations of a longer duration of action in humans.⁵⁰ However, carbimazole acts primarily as a prodrug of methimazole in both humans and cats.^{50,51} Car-

bimazole is used in the United Kingdom for cats with hyperthyroidism, and there are anecdotal reports that side effects such as blood dyscrasias are less common with carbimazole in cats in the UK compared with methimazole in cats in the US. This may be related to the finding that a 5 mg dose of carbimazole yields approximately 50% lower methimazole plasma concentrations than does a 5 mg dose of methimazole.⁵¹ There are no good studies comparing the side effect rates of methimazole to carbimazole, and because carbimazole is converted into methimazole, its use in cats with adverse reactions to methimazole is probably ill-advised.

Beta-Blockers

Beta-blockers can reduce the "sympathetic overdrive" characteristic of hyperthyroidism, to include tachycardia, arrhythmias, hyperactivity, and aggression. Propranolol has the additional potential benefit of reducing the conversion of T4 to T3.⁵² Therefore, propranolol (2.5 to 5 mg per cat three times daily) is useful for the short-term management of cats intolerant of methimazole, for which radioiodine or thyroidectomy are planned. As a nonselective beta-blocker, however, propranolol can lead to bronchospasm in cats with a prior history of reactive airway disease.^{53,54} Atenolol, a selective beta-1 blocker, is not associated with bronchospasm, and is preferred (3.125 or 6.25 mg per cat twice daily) for beta blockade in cats with a history of cough or bronchial changes on chest radiographs. Because neither of these treatments normalizes serum T4 or prevents weight loss, these drugs alone are not appropriate for long-term management of hyperthyroid cats.

Iodinated Contrast Agents

Iodinated contrast agents, such as ipodate and iopanoic acid, inhibit conversion of T4 to T3,⁵⁵ and have been advocated for use in hyperthyroid cats that do not tolerate methimazole. The efficacy of ipodate was evaluated in hyperthyroid cats,⁵⁶ at a dosage of 100 mg of calcium ipodate daily, titrated to 200 mg/d as needed. Eight out of 12 cats responded with weight gain, decreased in serum T3, and decreased heart rate. Serum T4 concentrations were unaffected. Ipodate (Oragrafin; 308 mg iodine per 500 mg calcium ipodate) is no longer marketed, but iopanoic acid (Telepaque; 333 mg iodine per 500 mg iopanoic acid)⁵⁷ and diatrizoate meglumine (Gastrograffin; 370 mg iodine per mL) have been used anecdotally in hyperthyroid cats at comparable doses. However, long term control may be poor, as the effects of these agents are often transient in both cats and humans.^{56,58} All iodine-containing agents will interfere with thyroid scanning and radioiodine therapy. In humans, iopanoic acid is discontinued 2 weeks before radioiodine therapy, with 94% of patients having a normalized thyroid scan, and response to radioiodine, by then.⁵⁹ Similar data are not available for cats.^{60,61}

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