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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 inappetance 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.

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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 excorations 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