Efficacy and safety of once versus twice daily administration of methimazole in cats with hyperthyroidism

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Objective—To determine whether once daily administration of methimazole was as effective and safe as twice daily administration in cats with hyperthyroidism.

Design—Randomized, nonblinded, clinical trial.

Animals—40 cats with newly diagnosed hyperthyroidism.

Procedure—Cats were randomly assigned to receive 5 mg of methimazole, PO, once daily (n = 25) or 2.5 mg of methimazole, PO, twice daily (1B). A complete physical examination, including measurement of body weight; CBC; serum biochemical analyses, including measurement of serum thyroxine concentration; and urinalysis were performed, and blood pressure was measured before and 2 and 4 weeks after initiation of treatment.

Results—Serum thyroxine concentration was significantly higher in cats given methimazole once daily, compared with cats given methimazole twice daily, 2 weeks (3.7 vs 2.0 µg/dL) and 4 weeks (3.2 vs 1.7 µg/dL) after initiation of treatment. In addition, the proportion of cats that were euthyroid after 2 weeks of treatment was lower for cats receiving methimazole once daily (54%) than for cats receiving methimazole twice daily (87%). Percentages of cats with adverse effects (primarily gastrointestinal tract upset and facial pruritus) were not significantly different between groups.

Conclusions and Clinical Relevance—Results suggest that once daily administration of methimazole was not as effective as twice daily administration in cats with hyperthyroidism and cannot be recommended for routine use. (J Am Vet Med Assoc 2003; 222:954–958)

Hyperthyroidism is a common endocrinopathy of middle-aged and older domestic cats, and in the United States, methimazole is commonly used for medical management of cats with hyperthyroidism. Methimazole is actively concentrated by the thyroid gland where it interferes with several steps in thyroid hormone synthesis, and it is very effective in restoring a euthyroid state in cats with hyperthyroidism. Although the drug is generally well tolerated, 10 to 20% of cats have experienced vomiting and anorexia during treatment, and potentially serious adverse effects such as skin excoriations, neutropenia, thrombocytopenia, and hepatopathy have occurred in 2 to 5% of treated cats.

The pharmacokinetics of methimazole following oral administration have been determined in healthy and hyperthyroid cats, and the plasma half-life is relatively short (approx 2 to 6 hours). Consistent with this short elimination half-life, it has been recommended that methimazole be administered every 8 to 12 hours in cats. However, although plasma concentration correlates with tissue concentration and duration of drug action for many drugs, this is not true for drugs such as methimazole that are actively concentrated at their target sites. For example, while the elimination half-life of methimazole in humans is 5 to 6 hours, methimazole may be detected in the thyroid gland and exert antithyroid effects for 24 hours or more. In accordance with this prolonged antithyroid effect, several studies in hyperthyroid human patients have shown similar rates of remission between once daily versus more frequent administration of methimazole. In addition, once daily dosing regimens are associated with better patient compliance.

Once daily dosing regimens for methimazole in cats with hyperthyroidism have not been critically evaluated. We hypothesized that if methimazole has a prolonged action in the thyroid gland in cats as it does in humans, then once daily dosing regimens would be as effective as dosing regimens involving more frequent administration. In addition, a once daily dosing regimen would be more convenient and would likely be associated with higher compliance. Therefore, the purpose of the study reported here was to compare the efficacy and safety of once versus twice daily administration of methimazole for treatment of hyperthyroidism in cats with newly diagnosed disease.

Materials and Methods

Client-owned cats with newly diagnosed, naturally occurring hyperthyroidism were eligible for inclusion in the study. The study design was approved by the institutional animal care and use committee, and all clients gave written informed consent. The diagnosis of hyperthyroidism was made on the basis of a high serum total thyroxine (T4) concentration.
concentration, determined by means of radioimmunoassay (reference range, 0.8 to 4.0 mg/dL), along with clinical signs of goiter, weight loss, tachycardia, polyuria, polydipsia, polyphagia, or hyperactivity. Only cats that had not previously been treated with methimazole were included in the study.

Cats were randomly assigned to receive 3 mg of methimazole, PO, once daily (SID group) or 2.5 mg of methimazole, PO, twice daily (BID group). At the time of enrollment in the study (week 0), age of each cat was recorded, and a physical examination, including measurement of body weight, CBC, serum biochemical profile, including measurement of serum T4 concentration; and urinalysis was performed. In addition, systolic blood pressure was measured with an indirect Doppler technique. Owners completed a questionnaire asking whether the cat had evidence of polyuria or polydipsia; changes in activity level or appetite; or vomiting, diarrhea, or facial excoriation.

Cats were reevaluated after 2 and 4 weeks of methimazole treatment. At that time, the physical examination, CBC, serum biochemical profile, urinalysis, and blood pressure measurement were repeated, and owners again completed the questionnaire. Blood was obtained for measurement of serum T4 concentration prior to administration of the next scheduled dose of methimazole for each cat (ie, approx 12 hours after pill administration for cats in the BID group and approx 24 hours after pill administration for cats in the SID group).

Criteria for removal of cats from the study included development of anemia, thrombocytopenia, neutropenia, or hyperbilirubinemia; a 2-fold increase (compared with week-0 values) in serum alanine aminotransferase (ALT) or alkaline phosphatase (ALP) activity; an increase in serum creatinine concentration to > 3.0 mg/dL, with clinical signs of illness; or persistent vomiting, persistent anorexia, or facial excoriation. The antihypertensive agent amlodipine (0.625 mg, PO, q 24 h)15 was prescribed, according to clinician discretion, for cats with systolic blood pressure > 180 to 200 mm Hg.15 Cats treated with amlodipine were not included in comparisons of blood pressure responses between groups.

Data were compared between groups with Mann-Whitney-Wilcoxon rank sum (numerical data) or χ2 (categorical data) tests; all statistical analyses were performed with commercial software.3 Changes in clinical parameters over time were evaluated with a Friedman 2-way ANOVA by ranks followed by pairwise comparisons with the Wilcoxon sign rank test.12 Correlations between pre- and posttreatment laboratory values were examined with z tests. For all analyses, values of P < 0.05 were considered significant. Data are reported as medians with observed ranges.

Results

Cats—Forty cats were enrolled in the study over a 22-month period. In 1 cat in which serum total T4 concentration was high normal (4.0 µg/dL) at the time of enrollment, the diagnosis of hyperthyroidism was confirmed on the basis of palpable enlargement of the thyroid gland, consistent clinical signs, and a high serum T4 concentration prior to referral. Twenty-five cats were randomly assigned to the SID group (3 mg of methimazole, PO, once daily), and 15 were assigned to the BID group (2.5 mg of methimazole, PO, twice daily).

There were no significant differences between groups in regard to baseline (week 0) serum T4 concentration, age, body weight, or daily dosage of methimazole (Table 1). Similarly, there were no significant differences between groups in regard to baseline heart rate; blood pressure; serum urea nitrogen, creatinine, and bilirubin concentrations; serum ALT and ALP activities; and urine specific gravity. One cat (SID group) was removed from the study by its owner after 2 weeks because of poorly controlled hyperthyroidism; serum total T4 concentration after 2 weeks of treatment with methimazole in this cat was 7.4 µg/dL. In a second cat (SID group), methimazole administration was discontinued by the owner prior to the 2-week recheck, reportedly because of gastrointestinal upset, but no evaluation could be performed.

Overall efficacy of methimazole administration—When all cats were considered together, median serum total T4 concentration after 2 weeks of methimazole treatment was significantly (P < 0.001) less than median baseline concentration (Table 1). However, median concentration after 4 weeks of treatment was not significantly different from median concentration after 2 weeks of treatment. By week 2, 26 of 39 cats (67%) were euthyroid (serum T4 concentration < 4 µg/dL), and by week 4, 23 of 29 (79%) were euthyroid. Pretreatment serum T4 concentration was significantly (r = 0.59; P < 0.001) correlated with serum T4 concentration after 4 weeks of methimazole treatment. Cats that were still hyperthyroid after 4 weeks of methimazole treatment had significantly (P = 0.04) higher pretreatment serum T4 concentrations (median, 10.8 µg/dL; range, 6 to 20 µg/dL) than did cats that were euthyroid after 4 weeks of methimazole treatment (median, 6.4 µg/dL; range, 4 to 16.1 µg/dL).

Six of 36 (17%) cats were hypertensive (indirect systolic blood pressure ≥ 180 mm Hg) at the time of enrollment in the study. Four cats with initial blood pressures > 200 mm Hg that were not treated with amlodipine were still hypertensive after 2 weeks of methimazole treatment, even though serum T4 concentrations were within reference limits.

Although body weight did not significantly increase over the study period, median heart rate did significantly (P = 0.002) decrease from week 0 to week 2 (Table 1). Similarly, serum ALT and ALP activities were significantly (P < 0.001) decreased by week 2, compared with week-0 values.

Efficacy of once versus twice daily administration—After 2 and 4 weeks of methimazole treatment, serum T4 concentration was significantly (P = 0.005 and 0.01, respectively) higher in cats in the SID group, compared to cats in the BID group (Table 1). Of the 24 cats treated once daily and reexamined 2 weeks later, only 13 (54%) were euthyroid after 2 weeks of treatment, compared with 13 of the 15 cats (87%) treated twice daily (P = 0.04). After 4 weeks of treatment, the percentage of cats treated once daily that were euthyroid (12/17; 71%) was no longer significantly (P = 0.17) different from the percentage of cats treated twice daily that were euthyroid (11/12, 92%). There were no significant differences between groups at any time in regard to heart rate, blood pressure, or body weight.

Overall adverse effects—Overall, 17 of the 39 cats evaluated (44%) developed adverse effects attributed to methimazole administration during the 4 weeks of the study. All of these cats but 1 with mild equivocal pruritus had the drug discontinued at the time of adverse reaction. Nine cats (23%) had signs of gas-
Urine specific gravity did not change over time. Serum urea nitrogen during the 4-week observation period.

Median serum creatinine concentration rose modestly but significantly (P < 0.001) after 2 weeks of methimazole treatment (Table 1), but serum urea nitrogen concentration did not change significantly (P = 0.1) over time. Urine specific gravity did not change over time, and methimazole administration was not discontinued in any cat because of worsening azotemia.

Adverse effects of once versus twice daily administration—Administration of methimazole was discontinued because of adverse effects in 10 of the 24 cats (42%) treated once daily. This was not significantly different from the percentage of cats treated twice daily that developed adverse gastrointestinal tract effects (7/24; 29%) was not significantly different (P = 0.25) from the percentage of cats treated twice daily that did not receive methimazole administration was discontinued because of adverse effects (6/15; 40%). The percentage of cats treated once daily that developed adverse gastrointestinal tract upset was 7% (7/24) and severe enough to warrant discontinuation of drug administration was both treated with methimazole once daily and 2 cats (5%) developed neutropenia. None of the cats developed anemia or thrombocytopenia during the 4-week observation period.

Of the 4 cats that developed evidence of hepatopa-thy, 1 in the SID group and 2 in the BID group developed >3-fold increases in ALT activity despite reductions in serum total T4 concentrations, which was considered suggestive of drug-associated hepatocellular damage.

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Discussion

Results of the present study suggested that once daily administration of methimazole was not as effective at restoring a euthyroid state as twice daily administration in cats with hyperthyroidism. Serum T₄ concentration was significantly higher after 2 and 4 weeks of treatment in cats treated once daily, compared with cats treated twice daily, and a significantly lower percentage of cats treated once daily were euthyroid by the end of the second week of treatment. This is in contrast to results of a study involving human patients with Graves disease, in which time to euthyroidism was not significantly different between those treated once daily and those treated twice daily. Further, results of our study do not support the hypothesis that methimazole has a long (24 hours or more) duration of action in the thyroid gland of hyperthyroid cats. The intrathyroidal residence time of methimazole in cats has not been determined; however, it has been observed that following discontinuation of methimazole treatment, hyperthyroid cats have rebound increases in serum T₄ concentrations within 48 hours.³

The daily dose of methimazole used in this study was only 5 mg/cat, which was substantially lower than published recommendations.³,¹¹ This low dose was chosen because cats were in a relatively early stage of the disease at the time hyperthyroidism was diagnosed (median T₄ concentration, 7.0 µg/dL), compared with cats in which hyperthyroidism was diagnosed 15 years ago (mean T₄ concentration, 12.1 µg/dL),³ and because of the recently recognized risk of renal decompensation during treatment.¹⁴,¹⁵ The overall efficacy in our study (23/29 cats [79%] euthyroid by week 4) was comparable to that reported³ for cats treated during the 1980s at a dosage of 10 to 15 mg of methimazole/d (87% euthyroid by 2 to 4 weeks). Thus, a dosage of 5 mg of methimazole/d (divided or not) would appear to be efficacious for most cats with mild to moderate hyperthyroidism. However, higher pretreatment serum T₄ concentrations were associated with a failure to become euthyroid in this study, suggesting (as would be expected) that cats with high pretreatment serum T₄ concentrations are likely to require dosages of methimazole higher than 2.5 mg twice daily.

It is not certain from this study whether similar differences in efficacy would be seen with the use of higher dosages of methimazole (eg, 10 mg once daily vs 5 mg twice daily). It is certainly possible that a higher total daily dosage would result in better efficacy even with once daily administration, because thyroid peroxidase would likely be exposed to inhibitory drug concentrations for longer periods during each dosing interval. However, in those cats with high serum T₄ concentrations, the thyroid glands are likely to be larger, and the total mass of thyroid peroxidase to be inhibited is likely to be greater. Therefore, we hypothesize that similar differences in efficacy would be observed between once versus twice daily dosing regimens, even with higher dosages of methimazole.

Four cats in the present study with clinically important hypertension (indirect Doppler systolic blood pressure > 200 mm Hg) were not treated with amlodipine initially in the belief that restoration of euthyroidism would resolve hypertension. However, these 4 cats were still hypertensive after 2 weeks of methimazole treatment despite normalization of serum T₄ concentrations. Although none of these cats developed overt complications of hypertension during the first 2 weeks of the study, this finding suggests that clinicians should not rely on antithyroid treatment alone to resolve hypertension in cats with hyperthyroidism.

The percentage of cats with adverse effects attributable to methimazole administration in the present study (17/39; 44%) was higher than that reported previously for a large group of hyperthyroid cats treated with methimazole at a dosage of 5 mg, PO, every 8 or 12 hours (18%). In both studies, signs of gastrointestinal tract upset were the most common adverse effect, and the higher incidence of adverse effects in the present study may have been attributable to increased vigilance by both clinicians and owners given the prospective study design. In addition, as dictated by our study design, cats that only had gastrointestinal tract upset were removed from the study without first attempting to decrease the dosage of methimazole. However, after withdrawal from the study, some of these cats were subsequently treated with methimazole at a lower dosage without complications while awaiting radiiodine treatment (data not shown).

The incidence of hepatopathy in our study (4/39; 10%) was also higher than that reported previously (1.9%), even among cats treated with methimazole at higher dosages. Likely reasons for this difference include the small sample population in the present population and, more importantly, the decision in the present study to consider cats with increases in serum ALT activity as having hepatopathy, regardless of whether they had any clinical abnormalities. Three cats in the present study developed > 3-fold increases in ALT activity, which was considered suggestive of drug-associated hepatocellular damage. The mechanism of this hepatopathy is not well defined, but it may be mediated by an oxidative metabolite that is detoxified by glutathione.¹⁶

Another interesting finding in this study was the relatively high incidence of facial excoriation among cats in this study (6/39; 15%), compared with the incidence in a previous study of cats treated with methimazole at a dosage of 5 mg, PO, every 8 to 12 hours (2.3%). This difference could again be attributable to bias caused by the smaller sample size in our study or to greater vigilance on the part of clinicians and owners. Another possible explanation for the apparently higher incidence of facial excoriation in this study would be a change in the available formulations of methimazole over time; however, in both this study and the previous study, Tapazole was used exclusively.

In initial analyses of data from the first 12 cats enrolled in the present study, we found a significantly higher incidence of facial excoriation among cats treated once daily than among cats treated twice daily; however, this difference was no longer significant as more cats were recruited. Initially, we attributed the higher incidence of facial excoriation among cats treated once daily to the higher peak serum methimazole concentra-
tions associated with once daily treatment. However, cats treated with 5 mg of methimazole 2 to 3 times daily in a previous study did not have a high incidence of facial excoriation. In addition, no difference in the incidence of skin rash has been reported between human patients treated with high and low dosages of methimazole, and pruritus and excoriation were not reported following administration of methimazole at a high dosage (40 mg/kg [18 mg/lb], IV) to dogs.

In summary, administration of 5 mg of methimazole once daily was not as effective in lowering serum T4 concentration as administration of 2.5 mg twice daily in cats with hyperthyroidism. Thus, although no significant differences in the incidence of adverse effects were found between once and twice daily administration, once daily administration of methimazole cannot be recommended for routine use in cats with hyperthyroidism.

aTapazole, Eli Lilly Co, Indianapolis, Ind.

References