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 (15). 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)
concentration, determined by means of radioimmunoassay (ref-
ence range, 0.8 to 4.0 mg/dL), along with clinical signs of
 goiter, weight loss, tachycardia, polyuria, polydipsia, polypha-
gia, 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 methi-
mazole, PO, once daily (SID group) or 2.5 mg of methima-
 zole, 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 measure-
 ment of serum T4 concentration; and urinalysis was per-
 formed. 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 methima-
zole 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 referral. Twenty-five cats were
 enrolled in the study. Four cats with initial blood
 pressures > 180/100 mm Hg were excluded. Twenty-one
 cats had history of blood pressure > 180/100 mm Hg at
 the time of enrollment in the study. Four cats with initial blood
 pressures > 200 mm Hg that were not treated with
 amiodarone were still hypertensive after 2 weeks of
 methimazole treatment, even though serum T4 concen-
 trations were within reference limits.

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 alka-
 line phosphatase (ALP) activity; an increase in serum creati-
nine concentration to > 3.0 mg/dL with clinical signs of ill-
 ness; or persistent vomiting, persistent anorexia, or facial
 excoriation. The antihypertensive agent amlodipine (0.625
 mg, PO, daily) was prescribed, according to clinician dis-
 cretion, for cats with systolic blood pressure > 180 to 200
 mm Hg.13 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 (cate-
gorical 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.14 Correlations between pre- and posttreatment
 laboratory values were examined with z tests. For all analy-
 ses, 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 con-
centration was high normal (4.0 µg/dL) at the time of
 enrollment, the diagnosis of hyperthyroidism was con-
firmed on the basis of palpable enlargement of the thy-
roid 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 methima-
zole, 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 concen-
tration, age, body weight, or daily dosage of methi-
mazole (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 7.8 µg/dL. In a sec-
 ond 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 treat-
 ment was significantly (P < 0.001) less than median base-
 line concentration (Table 1). However, median concen-
tration 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 concen-
tration was significantly (r = 0.59; P < 0.001) correlated
 with serum T4 concentration after 4 weeks of methima-
zole 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 treat-
 ment (median, 6.9 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
 amiodarone were still hypertensive after 2 weeks of
 methimazole treatment, even though serum T4 concen-
 trations 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 administra-
 tion—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 treat-
 ment, 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 euthy-
roid (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-
trointestinal tract upset, including 7 in which gastrointestinal tract upset was the only adverse effect and 2 in which gastrointestinal tract upset was seen in conjunction with facial excoriation. Six cats (15%) developed facial excoriations, 4 cats (10%) showed signs of hepatopathy, 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 hepatopathy, 1 in the SID group developed hyperbilirubinemia (3.4 mg/dL) and high serum ALP activity (997 U/L) after 4 weeks of treatment, which was considered suggestive of drug-induced cholestatic hepatopathy. Three cats (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.

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.

### Table 1—Results of clinical and biochemical evaluations in hyperthyroid cats treated with 5 mg of methimazole once daily or 2.5 mg twice daily

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cats treated once daily</th>
<th>Cats treated twice daily</th>
<th>All cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methimazole dosage (mg/kg/d)</td>
<td>1.15 (0.70–2.50)</td>
<td>1.22 (0.78–2.38)</td>
<td>1.22 (0.70–2.50)</td>
</tr>
<tr>
<td>Baseline data (week 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cats</td>
<td>25</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Age (y)</td>
<td>14 (11–19)</td>
<td>13 (7–19)</td>
<td>14 (7–19)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>4.4 (2.0–7.1)</td>
<td>4.1 (2.1–6.4)</td>
<td>4.1 (2.0–7.1)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>200 (160–240)</td>
<td>210 (150–250)</td>
<td>208 (150–250)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>155 (120–225)</td>
<td>148 (130–214)</td>
<td>152 (120–226)</td>
</tr>
<tr>
<td>Serum T4 (µg/dL)</td>
<td>7.7 (4.0–20.0)</td>
<td>6.4 (4.1–16.1)</td>
<td>7.0 (4.0–20.0)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>105 (41–896)</td>
<td>99 (44–331)</td>
<td>104 (41–896)</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>60 (26–199)</td>
<td>64 (20–134)</td>
<td>65 (20–199)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3 (0.6–3.0)</td>
<td>1.3 (0.5–2.5)</td>
<td>1.3 (0.5–3.0)</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dL)</td>
<td>24 (16–60)</td>
<td>25 (19–51)</td>
<td>24 (16–60)</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.032 (1.015–1.051)</td>
<td>1.032 (1.017–1.050)</td>
<td>1.032 (1.015–1.051)</td>
</tr>
</tbody>
</table>

After 2 weeks of treatment

| No. of cats                | 24                      | 15                       | 39       |
| Body weight (kg)          | 4.5 (1.8–6.4)           | 4.3 (2.2–6.4)            | 4.3 (1.8–6.4) |
| Heart rate (beats/min)    | 190 (140–220)           | 190 (160–240)            | 190 (140–240)* |
| SBP (mm Hg)               | 155 (115–210)           | 155 (125–280)            | 155 (115–280) |
| Serum T4 (µg/dL)          | 3.7 (1.0–8.6)           | 2.0 (0.5–9.1)*           | 2.8 (0.5–9.1)* |
| ALT (U/L)                 | 71 (30–429)             | 66 (38–633)              | 69 (30–633)* |
| ALP (U/L)                 | 54 (18–117)             | 42 (17–117)              | 47 (17–117) |
| Creatinine (mg/dL)        | 1.5 (0.7–3.6)           | 1.8 (0.8–3.2)            | 1.6 (0.7–3.6)* |
| Urea nitrogen (mg/dL)     | 25 (17–59)              | 31 (22–59)               | 28 (17–59) |
| Urine specific gravity    | 1.030 (1.012–1.050)     | 1.034 (1.017–1.060)      | 1.032 (1.012–1.060) |

After 4 weeks of treatment

| No. of cats                | 17                      | 12                       | 29       |
| Body weight (kg)          | 4.4 (1.9–6.3)           | 4.4 (2.1–5.6)            | 4.4 (1.9–6.3) |
| Heart rate (beats/min)    | 200 (160–232)           | 200 (150–240)            | 200 (150–240) |
| SBP (mm Hg)               | 157 (110–176)           | 150 (120–208)            | 150 (110–208) |
| Serum T4 (µg/dL)          | 3.2 (0.5–11.6)          | 1.7 (0.5–4.3)*           | 2.8 (0.5–11.6)* |
| ALT (U/L)                 | 66 (37–1219)            | 60 (30–368)              | 63 (30–1219) |
| ALP (U/L)                 | 59 (22–997)             | 46 (24–125)              | 55 (22–997) |
| Creatinine (mg/dL)        | 1.4 (0.6–3.0)           | 1.8 (0.6–3.1)            | 1.6 (0.6–3.1) |
| Urea nitrogen (mg/dL)     | 25 (10–48)              | 29 (19–58)               | 27 (10–58) |
| Urine specific gravity    | 1.031 (1.015–1.051)     | 1.032 (1.017–1.050)      | 1.032 (1.015–1.051) |

Data are given as median (range).

*Significantly (P < 0.05) different from baseline (week 0) value. †Significantly (P < 0.05) different from value for the other treatment group.

SBP = Systolic blood pressure, measured with an indirect Doppler technique. ALT = Serum alanine aminotransferase activity. ALP = Serum alkaline phosphatase activity.

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 in which methimazole administration was discontinued because of adverse effects (6/15; 40%). The percentage of cats treated once daily that developed adverse gastrointestinal tract effects (7/24; 29%) was not significantly different (P = 0.23) from the percentage of cats treated twice daily that did (2/15; 13%). There were no significant differences between groups at any time in regard to serum urea nitrogen, creatinine, or bilirubin concentration; urine specific gravity; or serum ALT or ALP activity (Table 1).

Of the 6 cats that developed facial excoriation during the study, all but 1 were in the SID group. Overall, 5 of 24 (21%) cats treated with methimazole once daily developed facial excoriation, compared with 1 of 15 (7%) cats treated twice daily, but this difference was not significant. The 2 cats that developed neutropenia severe enough to warrant discontinuation of drug administration were both treated with methimazole twice daily; neutrophil counts in these cats after 4 weeks of treatment were 0.070 × 10³ and 0.910 × 10³ neutrophils/µL.
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.

The daily dose of methimazole used in this study was only 5 mg/cat, which was substantially lower than published recommendations. 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), and because of the recently recognized risk of renal decompensation during treatment. The overall efficacy in our study (23/29 cats [79%] euthyroid by week 4) was comparable to that reported 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 radioiodine treatment (data not shown).

The incidence of hepatopathy in our study (4/39; 10%) was also higher than that reported previously (1.5%), 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.

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.

References