Serum Concentrations of Methimazole in Cats After a Single Oral Dose of Controlled-Release Carbimazole or Sugar-Coated Methimazole (Thiamazole)*

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CLINICAL RELEVANCE

Methimazole (thiamazole) is an antithyroid drug commonly used to treat feline hyperthyroidism. It is routinely given twice daily. Carbimazole is a methimazole derivative that is rapidly metabolized to methimazole in vivo. A controlled-release tablet for once-daily carbimazole therapy has recently been developed in an attempt to improve compliance during medical management of feline hyperthyroidism. The results of a crossover study in six cats suggest that the pharmacokinetics of methimazole with a single dose of this controlled-release tablet may be similar to those with a single dose of a sugar-coated methimazole tablet when the two drugs are given at an equimolar dose. The mean half-lives were nearly identical (3.12 hours, sugar-coated methimazole tablets; 3.28 hours, controlled-release carbimazole tablets). The serum concentrations of methimazole at 24 hours were 21.7 ± 28.9 ng/mL in the cats treated with 5-mg sugar-coated methimazole tablets and 28.7 ± 37 ng/mL in the cats treated with 10-mg carbimazole tablets (which provide approximately 25% more methimazole after conversion to the active metabolite).

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**INTRODUCTION**

Hyperthyroidism is the most common endocrine disorder in middle-aged and older domestic cats. The treatment of choice for any individual cat depends on factors such as age, underlying health problems, and owner preference. Medical management with the antithyroid drug methimazole or carbimazole has become an attractive option, either before surgical/radioiodine therapy or for long-term management. Medical management is a relatively easy and inexpensive option that requires no specialized surgical skills, radiopharmaceutical license, or facilities and has few contraindications.

Methimazole and carbimazole are thioureylenedrugs that inhibit the peroxidase-catalyzed reactions involved with thyroid hormone synthesis. These two drugs possess the same active ingredient; carbimazole is rapidly metabolized to methimazole in vivo. Conversion is relatively complete, although the heavier molecular weight of carbimazole means that an approximately 1.6-fold larger dose of carbimazole is required to achieve equimolar concentrations of methimazole. For example, 8 mg of carbimazole must be given to equal 5 mg of methimazole. When molar differences between carbimazole and methimazole are taken into account, there is no difference in the pharmacokinetics of methimazole.

Owner compliance with treatment is an important aspect of medical management for feline hyperthyroidism. Carbimazole tablets licensed for human use release carbimazole rapidly and result in a relatively short half-life of methimazole in feline plasma; therefore, owners must dose cats two to three times daily. Methimazole is also typically administered in divided doses, although once-daily dosing can be effective during maintenance therapy, possibly due to enhanced residence time within the thyroid. In an attempt to improve compliance, a controlled-release carbimazole tablet has been developed for once-daily dosing. The objective of the current study was to compare methimazole pharmacokinetics after a single oral dose of either a controlled-release carbimazole tablet or a sugar-coated methimazole tablet in cats fed at the time of treatment administration. Both formulations are approved for use in cats.

**MATERIALS AND METHODS**

The test facility (Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ireland) supplied four male and four female cats that were acclimated for 1 week before study initiation. All eight cats had been vaccinated and dewormed according to current standard operating procedures (SOPs) at the test facility. The cats were examined by a veterinarian on the day of selection (study day −7) and again on the day before study initiation (study day −1). Six clinically healthy cats (3 males and 3 females) were included in the study.

The included cats had not been used in a pharmacokinetics study or any study in which there was significant blood loss for at least 3 months before study day −7. The cats had not been given any medication (excluding routine deworming and vaccination) for at least 2 weeks before selection on study day −7 and had not received methimazole (thiamazole), carbimazole, or any similar compound for at least 4 weeks before selection. On study day −1, the three males ranged in age from 13.4 to 14.5 (mean: 14.1) months and weighed 4.1 to 4.4 kg. The three female cats ranged in age from 7.4 to 14.2 (mean: 10.1) months and weighed 3.3 to 3.4 kg. All cats were European mixed breed.

Each cat was housed in an individual cage under relatively uniform conditions (temperature, 17°C to 19°C; relative humidity, 39% to 60%) at the test facility. Routine feeding, wa-
tering, and cleaning were performed according to the current SOPs at the facility. Cats were fed a commercially available dry diet at the recommended rate of approximately 100 g once daily. Potable water was available ad libitum. A trained technician performed general health observations once daily on all cats throughout the acclimatization and study periods.

Study Design

This study was designed as a crossover trial, with cats randomly assigned to receive either a single 10-mg dose of controlled-release carbimazole (Vidalta, Intervet/Schering-Plough Animal Health; approved only in the United Kingdom at the time of submission) or a single 5-mg dose of methimazole (Felimazole Tablets, Dechra Veterinary Products; approved for use in Canada, the United States, and 18 European countries). Randomization was done by the investigator on study day –1 by random order numbers derived from Fisher and Yates tables. Cats were ranked from heaviest to lightest body weight within sex and were randomly allocated to groups. There was a 7-day washout period between treatments.

Each cat received a single dose of the assigned formulation at each treatment. All treatments consisted of whole, commercially available tablets that were administered orally approximately 1 hour after feeding. Immediately after the study drug was administered, approximately 5 mL of water was administered to facilitate swallowing. After administration of the tablet, cats were rewarded with a small amount of commercially available wet diet. Each cat was observed immediately and at 1 hour (±10 min) after administration to ensure that no cat vomited the tablet.

Blood Sampling

Blood samples (approximately 1 mL) for methimazole analysis were drawn via jugular venipuncture on study day 0 before treatment. Posttreatment samples were drawn at 45 and 90 minutes and at 3, 6, 12, 18, 24, 36, and 48 hours. Upon completion of the final sample collection (i.e., 48 hours) for each treatment, all cats received approximately 100 mL of 0.9% (w/v) physiologic saline solution subcutaneously to facilitate blood volume replacement.

Blood samples were placed into lithium heparin anticoagulant tubes and centrifuged within 1 hour of collection. The resulting plasma was divided into two aliquots of approximately equal volumes, which were stored at –17°C to –18°C within 1 hour after centrifugation. After completion of the study, aliquot 1 was dispatched on dry ice to a contract laboratory (Quotient Bioresearch Ltd, Cambridgeshire, United Kingdom) for methimazole analysis. Aliquot 2 was placed in long-term storage at –72°C to –80°C until after all data had been collected. All experimental and operational procedures for the analysis were performed in accordance with the SOPs at the contract laboratory. Samples were analyzed for methimazole concentration using a proprietary liquid chromatography–tandem mass spectrometry bioanalytical method that had been validated in accordance with guidance issued by the US Department of Health.

In general, the pharmacokinetics values for the two treatments were similar when differences in effective methimazole dose were taken into consideration.
and Human Services, Food and Drug Administration. The lower limit of quantification was 10 ng/mL. The upper limit of quantification was 800 ng/mL. Samples with initial concentrations above 800 ng/mL were diluted appropriately with blank feline plasma and reanalyzed. The analysts were masked to treatment group assignment of individual cats.

**Pharmacokinetic Analysis**

Data were analyzed using WinNonLin 5.2 (Pharsight, Mountain View, CA) employing a noncompartmental pharmacokinetic approach that uses the log-linear trapezoidal rule, as follows:

- $C_{\text{max}}$ (maximum concentration) and $t_{\text{max}}$ (time to maximum concentration) were obtained directly from the data.
- $\text{AUC}_{\text{inf}}$ (area under the curve extrapolated to infinity) was calculated as the sum of $\text{AUC}_{\text{last}}$ (truncated area under the concentration vs time curve) and $C_{\text{last}}/\lambda_z$ (concentration at the last sampling point/slope of the terminal phase [elimination rate constant]).
- The $\%\text{AUC}_{\text{extrp}}$ (percent extrapolated area under the curve) was calculated to verify that the extrapolation from $\text{AUC}_{\text{last}}$ to $\text{AUC}_{\text{inf}}$ was adequate.
- $\lambda_z$ was obtained from log-linear fitting of the terminal elimination phase.
- Half-life of the terminal elimination phase was obtained as $0.693/\lambda_z$.

Descriptive statistics include the arithmetic average, standard deviation, coefficient of variance (CV) and median, with the exception of the half-life. Because the half-life is a reciprocal parameter, the most appropriate summary measures of central tendency and interindividual variability are the harmonic mean and the pseudostandard deviation, respectively. The parameter least likely to be normally distributed is $t_{\text{max}}$, for which the most appropriate measures of central tendency and spread are the median and the range. Given the small sample size, no formal statistical analyses were planned for this study.

**Ethical Standards**

The plan for this study was reviewed and approved by the ethics committee at the test facility and was in full compliance with animal welfare requirements in Ireland. All experimental and operational procedures performed in relation to the animal phase of the study were carried out in accordance with the current SOPs at the test facility. Following study completion, all cats were returned to the colony at the test facility.

**RESULTS**

The test tablets were well tolerated by the...
cats during the course of the study. The general health of the cats remained good throughout the study, with the exception of one cat that was diagnosed with tracheitis/pneumonia, possibly caused by accidental inhalation of water after drug administration. This cat was treated with enrofloxacin and dexamethasone once daily for 3 days and was found to be clinically normal on study day 3 and thereafter.

Examination of the concentration–time curves for the two formulations (Figure 1) shows that methimazole reached an earlier and slightly higher peak when sugar-coated methimazole tablets were given compared with controlled-release carbimazole tablets but that drug concentrations appeared higher at 3 to 12 hours with the carbimazole tablets. Plasma concentrations of methimazole from the two formulations were similar thereafter, although drug concentrations remained slightly higher at 12 to 24 hours after administration of the carbimazole tablet. The mean AUClast and AUCinf for methimazole in carbimazole-dosed cats were approximately 26% higher than those in cats dosed with a sugar-coated methimazole tablet (Table 1), consistent with the 25% higher dose of methimazole given with the carbimazole tablet compared with the methimazole tablet on an equimolar basis. The mean AUClast and AUCinf were more variable for the carbimazole tablet than for the sugar-coated methimazole tablet. The CVs were approximately 22% and 10% for the carbimazole and methimazole tablets, respectively.

The mean Cmax was slightly higher for the sugar-coated methimazole tablet than for the carbimazole tablet (Table 1). The mean Cmax was more variable for the methimazole-dosed cats than for the carbimazole-dosed cats, with CVs of 43% and 22%, respectively.

The half-life of methimazole was nearly identical for both formulations (~3 hours). The time to last measurable concentration (tlast) was only slightly shorter for the sugar-coated methimazole tablets than for the controlled-release carbimazole tablets (23 and 24 hours, respectively). The number of cats with methimazole concentrations above the level of detection at 12, 18, and 24 hours was 6, 6, and 3, respectively, for the sugar-coated methimazole tablets and 6, 6, and 4, respectively, for the controlled-release carbimazole tablets. The 24-hour concentration of methimazole was 21.7 ± 28.9 ng/mL in the methimazole-dosed cats and 28.7 ± 37 ng/mL in the carbimazole-dosed cats.

### TABLE 1. Pharmacokinetic Parameters After a Single Dose of Either a Controlled-Release Carbimazole Tablet or a Sugar-Coated Methimazole Tablet

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Carbimazole 10 mg</th>
<th>Methimazole 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>1198 ± 262 ng/mL</td>
<td>1325 ± 574 ng/mL</td>
</tr>
<tr>
<td>tmax</td>
<td>3 (1.5–6) h</td>
<td>1.5 (0.75–12) h</td>
</tr>
<tr>
<td>λz</td>
<td>0.211 ± 0.37 h⁻¹</td>
<td>0.222 ± 0.05 h⁻¹</td>
</tr>
<tr>
<td>Half-life</td>
<td>3.28 ± 0.6 h</td>
<td>3.12 ± 0.7 h</td>
</tr>
<tr>
<td>AUClast</td>
<td>9352 ± 2140 ng*h/mL</td>
<td>7425 ± 733 ng*h/mL</td>
</tr>
<tr>
<td>tlast</td>
<td>24.6 ± 6 h</td>
<td>23 ± 7 h</td>
</tr>
<tr>
<td>AUCinf</td>
<td>9479 ± 2096 ng*h/mL</td>
<td>7531 ± 732 ng*h/mL</td>
</tr>
<tr>
<td>%AUCexp</td>
<td>0.015% ± 0.009%</td>
<td>0.014% ± 0.011%</td>
</tr>
</tbody>
</table>

*All values are mean ± SD unless otherwise indicated.

*Median (range).

AUCinf = area under the curve extrapolated to infinity, AUClast = truncated area under the concentration vs time curve, %AUCexp = percent extrapolated area under the curve, Cmax = maximum concentration, λz = slope of the terminal phase, tlast = time to last measurable concentration, tmax = time to maximum concentration.
DISCUSSION

In general, the pharmacokinetics values for the two treatments were similar when differences in effective methimazole dose were taken into consideration. As both manufacturers caution against splitting or crushing tablets, only whole tablets were administered. Carbimazole is metabolized to methimazole at a ratio of 1.6:1, so 10 mg of carbimazole is equivalent to approximately 6.25 mg of methimazole. Therefore, the 10-mg carbimazole treatment delivered approximately 25% more methimazole than the 5-mg methimazole treatment, which is consistent with the 26% higher AUC values associated with the carbimazole group.

The most interesting clinical finding of this study is that the mean half-lives for methimazole with both formulations were nearly identical (3.12 and 3.28 hours for sugar-coated methimazole tablets and controlled-release carbimazole tablets, respectively), and the median t<sub>max</sub> values were similar (1.5 and 3 hours for sugar-coated methimazole tablets and controlled-release carbimazole tablets, respectively). This was unexpected because the plasma half-life of a controlled-release formulation would be anticipated to be significantly longer than that for a “standard” tablet. Indeed, Frénais et al. reported a mean plasma methimazole half-life of 9 hours after a single dose of a 15-mg controlled-release carbimazole tablet given to fasted cats. In contrast, in our study, the mean half-lives, median t<sub>max</sub> values, and mean t<sub>last</sub> values were similar for the sugar-coated methimazole tablets and the controlled-release carbimazole tablets.

The methimazole measurements in the current study varied somewhat from those reported in the literature. For example, Peterson and Aucoin reported AUC, C<sub>max</sub>, and half-life values that were approximately 30% to 40% higher than those reported for a comparable 5-mg oral methimazole tablet in the current study. These differences may represent statistical or interlaboratory variation or difference in test conditions. Cats in the current study were younger (approximately 1 year of age) than those used in other studies (2 to 6 years of age). Similarly, study drugs were administered 1 hour after feeding in the current study, but the prandial state is not clear in the Peterson and Aucoin study. In other studies, drugs were given to fasted animals. Feeding has been shown to substantially increase AUC and C<sub>max</sub> values after administration of controlled-release carbimazole.

While the relatively short plasma half-lives reported in the current study would seem to support either once or twice daily dosing for either sugar-coated methimazole or controlled-release carbimazole tablets, methimazole accumulates in the thyroid gland so that antithyroid effects extend beyond (possibly up to 24 hours) the duration of elevated plasma levels. Antithyroid effects may also be partially attributable to a metabolite (3-methyl-2-thiohydantoin) that has a longer half-life as well as antithyroid activity. This may explain successful once-daily therapy in some cats with either formulation.

It should be noted that the results reported for the current study were for healthy, rather than hyperthyroid, cats. However, previous studies in people and cats suggest that the presence of hyperthyroidism should not substantially alter methimazole pharmacokinetics. The treatments were well tolerated by cats in the current study. One cat suffered mild respiratory problems, but this did not appear to be related to the study drug and had resolved after 3 days of treatment with antibiotics and corticosteroids. Treatment for this respiratory infection began 1 day after the initial treatment and ended 3 days before the second treatment, so it was unlikely to have had any substantive effect on methimazole pharmacokinetics.
RESULTS

Results from the current study suggest that controlled-release carbimazole and sugar-coated methimazole tablets may have similar pharmacokinetics when administered at equimolar doses to fed cats. The short half-life of 3 hours for both controlled-release carbimazole and sugar-coated methimazole tablets is consistent with current practice recommendations for divided daily dosing, although once-daily dosing may be appropriate for maintenance therapy in some animals.

ACKNOWLEDGMENTS

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REFERENCES