J Vet Intern Med 2011;25:1357–1365

The Efficacy and Safety of a Novel Lipophilic Formulation of Methimazole for the Once Daily Transdermal Treatment of Cats with Hyperthyroidism

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Background: Previous studies on transdermal methimazole have used pluronic lecithin organogel as the vehicle. This might not be the most suitable vehicle for a lipophilic drug, such as methimazole.

Hypothesis/Objectives: Once daily transdermal administration of a novel lipophilic formulation of methimazole is as safe and effective as oral carbimazole in treating hyperthyroidism in cats.

Animals: Forty-five client-owned cats diagnosed with hyperthyroidism.

Methods: Prospective study. Cats with newly diagnosed, untreated hyperthyroidism were treated with carbimazole (5 mg PO, q12h) or methimazole (10 mg) applied to the inner pinnae q24h. Cats were examined after 0, 1, 4, 8, and 12 weeks of treatment. Clinical signs, body weight, systolic blood pressure, hematologic, serum biochemical and urine parameters, total serum thyroxine concentrations (TT4), and serum methimazole concentrations were recorded.

Results: No significant differences between groups were detected at day 0. Both formulations were effective in treating hyperthyroidism. No significant differences were detected in thyroxine concentrations, body weight, blood pressure, heart rate, alkaline phosphatase, alanine aminotransferase, creatinine, urea, and urine specific gravity (USG) between groups. The serum methimazole concentrations correlated poorly with TT4-concentrations in both groups.

Conclusions and Clinical Importance: In this 12-week trial, once daily application of a novel formulation of transdermal methimazole applied to the pinnae was as effective and safe as twice daily oral carbimazole in the treatment of cats with hyperthyroidism. This novel formulation and transdermal application could have practical advantages to some pet owners.

Key words: Feline; Hyperthyroidism; Methimazole; Transdermal.

Benign hyperplasia of the thyroid is a very common condition in cats older than 6 years of age.[1,2] There are 3 treatment options for hyperthyroidism: thyroidectomy, radioactive iodine, or anti-thyroid drugs, such as carbimazole (Neomercazole or Vidalta) or methimazole (Tapazole).[3–8] Radioactive iodine has the fewest adverse effects and is the most efficacious of the treatments, but availability can be limited, upfront costs can be high, clients might not like radiation therapy, and cats with concurrent renal disease are not suitable candidates.[3,4,9,10]

Medical therapy might then be an attractive option for clients. Medical management is also recommended before surgery to stabilize the patient, and is often recommended before radioactive iodine to assess renal function.[11] The use of carbimazole or methimazole to medically manage cats with hyperthyroidism has been standard practice since the discovery of the disease in the early 1980s.[5,12–17] Carbimazole is a pro-drug of methimazole which is used as tablets to treat cats with hyperthyroidism in Europe, Australia, and New Zealand.[12,13,18] In New Zealand, the use of carbimazole to treat cats with hyperthyroidism is off-label, as the drug is not registered for veterinary use. In Europe, a once daily long-acting carbimazole tablet (Vidalta) has been registered for veterinary use, and the FDA recently approved methimazole for the treatment of cats with hyperthyroidism in the United States.[18–20]

Abbreviations:

HPLC	high performance liquid chromatography
PLO	pluronic lecithin organogel
TT4	total thyroxine
UA	urinalysis

However, some cats are notoriously hard to medicate with oral drugs and medical management of hyperthyroidism typically requires twice daily oral tablets. Because of this, many compounding pharmacies have started formulating drugs into gels, which are applied to the inner side of the cat's ear and are thought to be absorbed through the skin for systemic action.[21–37]

Not all drugs are suitable for transdermal penetration and only a few drugs have been studied in cats to determine whether they reach therapeutic concentrations after absorption by this route.[21–23,26,27,30,31] There are several factors that affect the transdermal delivery of drugs.[38] First, the molecule itself needs to be small (<500 Da), have few atoms available for hydrogen bonding, be lipophilic, and have a low melting point. The vehicle must be soluble enough for the drug to dissolve, and the drug itself needs to be able to diffuse through the subcutaneous lipids. For transdermal absorption, the drug must be highly lipophilic and formulated in the correct vehicle.[28]

All previous studies of transdermal methimazole in cats have used pluronic lecithin organogel (PLO) gel as

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Submitted May 10, 2011; Revised July 31, 2011; Accepted August 12, 2011.

10.1111/j.1939-1676.2011.00799.x

the vehicle, [24,25,29,39] however, methimazole is a lipophilic drug, and PLO gel might not be the most suitable vehicle for a lipid soluble drug.[38] A suitable vehicle should be soluble enough to contain the active drug without the drug precipitating out of solution.[38] As a vehicle for methimazole, PLO gel has problems with drug precipitation and a nonhomogenous texture to the gel developing.[25] Pharmacokinetic studies of methimazole in PLO gel showed that it was poorly absorbed when applied transdermally but did show clinical efficacy in some cats with repeated applications.[24,25,29,39]

The aim of this study was to compare, in a controlled and prospective clinical trial, the safety and efficacy of oral carbimazole, with a novel lipophilic formulation of transdermal methimazole applied to the pinnae once a day.

Materials and Methods

Inclusion Criteria

Client-owned cats with newly diagnosed, untreated, naturally occurring hyperthyroidism, that were suitable for medical treatment and had no clinically important other medical disease not attributable to hyperthyroidism, were eligible for the study. The study was approved by the Massey University Animal Ethics Committee and owners gave informed, written consent. Cats were diagnosed with hyperthyroidism based on a TT4 concentration greater than 3.9 μg/dL (50 nmol/L), measured by chemiluminescence (reference range 1.56–3.12 μg/dL, or 20–40 nmol/L), along with palpable goiter and clinical signs attributable to hyperthyroidism (weight loss, tachycardia, polyphagia, polydipsia, or hyperexcitability).

Exclusion Criteria

Cats were excluded from entering the trial if clinically important medical disease was present that was not attributable to hyperthyroidism. Cats were screened for the trial by one of the authors (KH) having verbal consultation with the referring veterinarian and a review of the cats' history, including laboratory tests. Cats were excluded during the trial if owners failed to return for rechecks; facial pruritis developed; clinical signs of illness occurred along with neutropenia ($<1.0 \times 10^9$/L); serum alanine aminotransferase (ALT) or alkaline phosphatase (ALP) activity increased more than twice the week 0 value; persistent clinical signs of vomiting and diarrhea occurred; or creatinine concentrations increased above 2.75 mg/dL (250 μmol/L) with clinical signs of illness. Cats were treated with amlodipine[a] (0.625 mg PO/day) for hypertension if the systolic blood pressure was greater than 180–200 mmHg on 2 consecutive visits, or if there was retinal hemorrhage present at the initial visit. These cats were excluded from the analysis of blood pressure.

Drug Administration

Forty-five cats were enrolled in the study from July 2007 to March 2009. This number was chosen on the basis of a power analysis based on a pilot study. Cats were alternately assigned to receive a starting dose of either oral carbimazole[b] (5 mg q12h) or 10 mg (0.1 mL) of the novel formulation of transdermal methimazole applied to the inner pinnae once daily. The transdermal methimazole was applied to the owner's gloved finger and then rubbed onto the nonhaired portion of the inner pinnae of alternate ears for each treatment. The 2 clinicians involved in the study (KH and DK) were not blinded to the treatment groups.

Methimazole Formulation

Methimazole for transdermal application was formulated by Bomac Laboratories Ltd, US patent number US 2010/0137389.[40] The novel transdermal formulation was composed of methimazole, carrier compounds (propylene glycol, polyethylene glycol 4000, dimethyl formamide, and cyclodextrin), and a combination of penetration enhancers selected from fatty acids, terpenes, pyrrolidones, a short chain alcohol, glycol ethers, acetins, and triglycerides. The methimazole was sourced from an approved source from a Good Manufacturing Practice certified company. Stability testing, performed under VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products) guidelines for the stability testing of new veterinary drug substances, had determined that this product was stable for 12 months after formulation.[40,41] The formulation was supplied in 1 mL syringes at 100 mg/mL.

Monitoring

Cats were evaluated at 0, 1, 4, 8, and 12 weeks after the start of treatment. At each evaluation, a physical examination was performed, systolic blood pressure was measured, body weight was recorded, and clients were asked to complete a questionnaire about their cat's improvement and tolerance of the drug (vomiting, diarrhea, appetite, facial pruritis, coat changes, weight loss) (Appendix 1). Blood and urine samples were obtained for a complete blood count,[c] serum chemistry,[d] urinalysis (UA)[e], TT4 concentrations,[f] and methimazole concentrations. Blood samples were collected 6–8 hours after carbimazole dose or 18–20 hours after a transdermal methimazole dose. The timing of blood sampling was standardized, but this timing was mainly determined by the practical availability of the cats and their owners and clinic operational hours. Laboratory testing was performed at an onsite referral laboratory (New Zealand Veterinary Pathology). Methimazole or carbimazole doses were adjusted at weeks 4, 8, and 12 aiming to maintain a TT4 concentration within the reference range of 20–40 nmol/L.

High Performance Liquid Chromatography (HPLC) Analysis of Methimazole from Serum

Sample Preparation. Whole blood samples from cats were allowed to clot for at least 30 minutes. Blood samples were stored overnight at 4°C and serum was prepared by centrifugation at $3{,}000 \times g$ for 5 minutes and the supernatant was collected. Serum was stored at −20°C until use. Proteins in the serum samples were removed by precipitation with methanol. To 100 μL of serum, 500 μL of ice-cold methanol was added and the sample was vortexed. Samples were incubated on ice for 30 minutes and then centrifuged at $10{,}000 \times g$ for 5 minutes. The supernatant was collected and then air dried on a heating block at 55°C. The dried samples were dissolved in 100 μL of mobile phase, vortexed and sonicated briefly, and centrifuged at $10{,}000 \times g$ for 10 minutes. The supernatant (100 μL) was collected and loaded into the auto sampler. All samples were prepared in duplicate for HPLC.

HPLC Methods. Samples were analyzed for HPLC as described earlier.[42] Samples were analyzed with a Shimadzu LC20VP system (Columbia, MD). The same HPLC conditions were used for all samples. Methimazole standards were run before all samples.

The mobile phase consisted of 0.1 M ammonium acetate, pH 4.0 in 5% (v/v) acetonitrile made up in MilliQ grade water (Millipore), and filtered with a 0.4 micron filter. The column was a Phenomenex (Torrance, CA) Luna C18, 150 × 4.6 mm, 5 micron, with a Phenomenex guard column.

For each run, 10 μL was injected at a flow rate of 0.6 mL/min, the oven set temperature was 30°C, and the detection wavelength was 252 nm. The run time was 15 minutes. The limit of quantitation was 75 ng/mL.

Intra-assay variation was ±3.1% at a 95% confidence level. Inter-assay variation at a 95% confidence level ranged between ±1.5% and 9.0% over the range of concentrations relevant to the study. Methimazole recovery from cat serum was calculated to be 83%.

Statistical Analyses

Data were analyzed by linear mixed model methodology that accounted for repeated measures on the same cat and associated correlated errors (nlme Package in R version 2.8.1.[g]). The model included the fixed effects of treatment (oral and transdermal), time (week of treatment), and their interaction and the random effect of cat within treatment. By the Akaike's information criterion, a compound symmetry error structure was determined as the most appropriate residual covariance structure for repeated measures over time within cat. Least squares means and their standard errors were obtained for each treatment for weeks 0, 4, 8, and 12.

Results

Fifty-three cats were screened for this study. Eight cats were ineligible for the trial as they did not meet inclusion criteria because of other medical diseases not attributable to hyperthyroidism. Forty-five cats with newly diagnosed, naturally occurring hyperthyroidism were enrolled in the study at Massey University Veterinary Teaching Hospital. Twenty-two cats received oral carbimazole at a starting dose of 5 mg q12h, and 23 cats received transdermal methimazole at a starting dose of 10 mg once a day. No clients declined enrollment after being assigned to specific treatment groups. Five cats died (three were euthanized) during the trial unrelated to drug therapy and were excluded from the statistical analysis. No significant differences between treatment groups were detected at day 0. Both drugs were effective in treating hyperthyroidism as determined by a reduction in TT4 concentrations (Fig. 1). Additional evidence of efficacy was demonstrated with an increase in body weight, a decrease in blood pressure (Table 1), and improvement in clinical signs (such as decreased appetite) in both groups. Repeated measurements of TT4 concentrations, weight, blood pressure, ALP, ALT, creatinine, urea, and USG showed no significant difference between treatment groups. Heart rate was significantly lower ($P = .05$) and hematocrit was significantly higher ($P = .02$) for the transdermal methimazole group compared to the oral group.

Methimazole Serum Concentrations

Methimazole was detected in the serum of cats from both the oral and transdermal groups after dosing

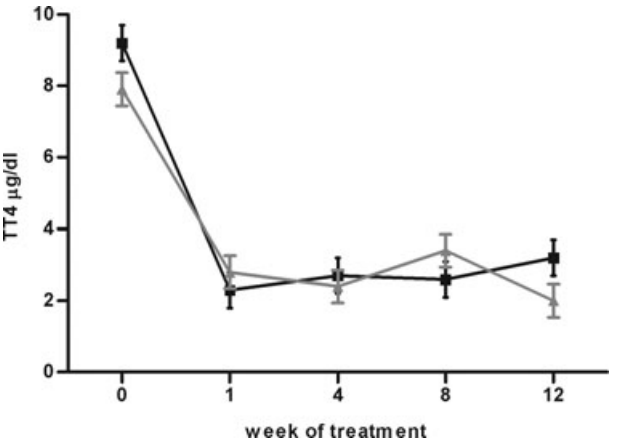

Fig 1. Mean serum total thyroxine concentrations with standard error bars, in 20 cats treated with oral carbimazole (■) and 20 cats treated with transdermal methimazole (▲).

(Fig. 2). However, methimazole concentrations correlated poorly with TT4 concentrations in both groups (Fig. 3).

Adverse Events

No cats that were enrolled in the trial were removed from the trial based on the exclusion criteria. However, 5 cats died during the study period, but none of the deaths were attributable to the drug therapy. In the oral carbimazole group, 1 cat was euthanized 8 weeks after the start of the study because of difficulty in eating. A necropsy revealed moderate renal disease; however, the exact cause of the difficulty in prehending food was undetermined. A 2nd cat with a heart murmur died acutely at week 2. A necropsy was not performed, but acute thrombotic disease was suspected from the owner's description. Two cats in the transdermal group were euthanized. The 1st cat developed pleural effusion and the 2nd cat had hind leg weakness. Necropsies revealed mediastinal lymphosarcoma and iliac thrombus, respectively. A 3rd cat in this group was euthanized at 8 weeks in accordance with owner's last will and testament. Six cats (3 in each group) developed IRIS (International Renal Interest Society) stage II kidney disease during the treatment trial. One cat in the transdermal methimazole group developed neutropenia at week 4 (day 30). A urine culture revealed no growth of bacteria, and FIV and FeLV tests were negative. The cat was clinically normal and never developed a fever. Transdermal methimazole was stopped for 7 days and prophylactic amoxicillin-clavulanic acid[h] (20 mg/kg PO q12h) was administered. The cat was monitored with clinical evaluations and a CBC and serum biochemistry at day 33, 37, and 44. At day 37, the cat was demonstrating severe signs of hyperthyroidism (polyuria, polydipsia, and polyphagia) and the TT4 concentration was severely increased (>15 μg/dL, 193 nmol/L). Transdermal methimazole was reinstated at half the original dose (5 mg once a day), and amoxicillin-clavulanic

Table 1. Selected clinical parameters in cats with hyperthyroidism, treated with oral carbimazole or transdermal methimazole over a 12-week study period. Data are given as least squares means (standard error) obtained from repeated measures analysis.

Variable	Oral					Transdermal				
Week of Treatment	0	1	4	8	12	0	1	4	8	12
Age (years)	14					12.5				
Body weight (kg)	3.77	3.84	3.89	4.01	4.06	3.75	3.78	3.85	3.88	3.88
(std error)	(0.23)	(0.23)	(0.23)	(0.23)	(0.23)	(0.23)	(0.23)	(0.23)	(0.23)	(0.24)
HR (beats/min)	207	199	182	185	178	194	184	179	173	170
(std error)	5.9	6.0	5.9	6.0	6.2	6.0	6.9	7.2	7.3	7.3
SAP (mmHg)	172	170	157	160	144	182	172	160	162	158
(std error)	7.3	7.3	7.4	7.3	7.4	7.8	7.9	7.8	7.9	7.8
TT4 μg/dL (nmol/L)	9.2 (118)	2.2 (29.00)	2.7 (34.2)	2.6 (33.2)	3.2 (40.9)	7.9 (101.5)	2.8 (36.5)	2.4 (30.4)	3.3 (42.5)	2.3 (29.5)
(std error)	0.53	0.53	0.53	0.53	0.53	0.53	0.53	0.53	0.53	0.53
ALT (IU/L)	155	112	70	64	65	145	94	99	104	87
(std error)	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9
ALP (IU/L)	84	62	35	35	35	83	66	50	50	45
(std error)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Creatinine mg/dL (μmol/L)	1.0 (95)	1.1 (103)	1.3 (121)	1.4 (127)	1.4 (124)	0.9 (84)	0.9 (87)	1.1 (101)	1.2 (107)	1.1 (104)
(std error)	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Urea mg/dL (mmol/L)	29.4 (10.5)	30.1 (10.7)	33.2 (11.8)	37.9 (13.5)	35.4 (12.7)	27.5 (9.8)	30.3 (10.8)	32.1 (11.5)	31.5 (11.2)	34.7 (12.4)
(std error)	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Hematocrit (L/L)	0.386	0.362	0.357	0.342	0.351	0.412	0.402	0.393	0.383	0.370
(std error)	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012
WBC ($x10^9$/L)	9.7	10.0	10.3	10.9	9.6	11.5	11.8	10.9	10.7	10.3
(std error)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
USG	1.037	1.039	1.042	1.037	1.040	1.037	1.040	1.041	1.036	1.036
(std error)	0.003	0.003	0.003	0.003	0.004	0.003	0.004	0.004	0.004	0.004

HR, heart rate; SAP, systolic arterial pressure; ALT, alanine aminotransferase; ALP, alkaline phosphatase; USG, urine specific gravity.

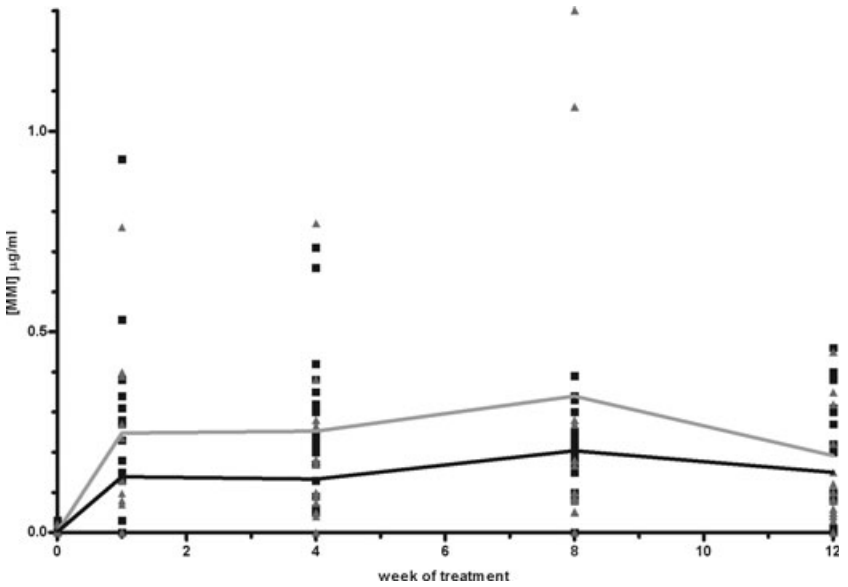

Fig 2. Mean and individual serum methimazole concentrations [MMI] in 20 cats treated with oral carbimazole (■) and 20 cats treated with transdermal methimazole (▲).

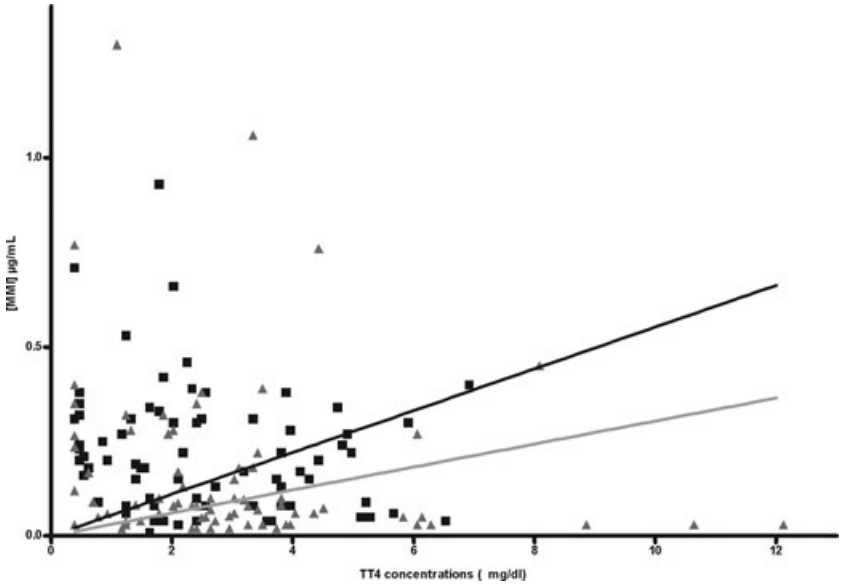

Fig 3. Correlation was poor between serum methimazole concentrations [MMI] and total thyroxine concentrations (TT4) in cats receiving oral carbimazole (po) (■) ($r^2 = 0.2$) and transdermal methimazole (td) (▲) ($r^2 = 0.16$). Data from cats at 4, 8, and 12 weeks of treatment are pooled.

acid was continued. At day 44, the neutrophil count had returned to normal, antimicrobial therapy was discontinued, and the cat had no further problems during the trial. A 2nd cat in the transdermal methimazole group developed acute vomiting and anorexia at week 2 of the study. Clinical examination revealed mild abdominal pain and mild increase in ALT (130 IU/L reference range 0–100 IU/L), abdominal ultrasonography was normal, and hepatic fine needle aspirate revealed normal hepatic cells. A clinical diagnosis of acute gastritis was made, and the diet was changed to a low allergenic diet.[1] No changes were made to the transdermal methimazole dose. Within 48 hours, the cat was clinically normal. At week 4, the cat was clinically normal and serum activity of hepatic enzymes had decreased (ALT 114 IU/L [reference range 0–100 IU/L]). One cat in the oral carbimazole group developed vomiting at week 2. Clinical examination was normal and CBC and serum chemistry was normal. The vomiting ceased when the carbimazole was stopped for 2 days. Vomiting started again when carbimazole was reintroduced at 5 mg twice a day. Vomiting was

controlled when carbimazole was decreased to 5 mg every 2nd day in the morning and 5 mg daily at night for 4 weeks (week 4). The carbimazole was then reinstated at 5 mg twice daily at week 8 with no adverse effects. No cats in the transdermal methimazole group developed pruritis or erythema of the pinnae.

Dose Modifications

Eight cats in the transdermal group had dose modifications (Table 2). Five cats had a dose reduction and 3 cats had a dose increase. Thirteen cats in the oral carbimazole had dose modifications, with 9 requiring a decrease in the dose and 4 requiring an increase (Table 3). One cat in the transdermal methimazole group never achieved a TT4 concentration (range 4.0–10.7 μg/dL, 51–137 nmol/L) within the reference range, and clinical signs of hyperthyroidism were never completely controlled, although an improvement was noticed. The owner was repeatedly shown how to apply the ointment and questioned over compliance. The owners stated that they were applying the ointment daily, although the investigators queried this. When the trial was completed, the owners were offered a change to oral carbimazole or radioactive iodine and the cat responded to radioactive iodine treatment.

Table 2. Dose of transdermal methimazole administered to cats in the study on the efficacy and safety of a novel lipophilic formulation of methimazole for the once daily transdermal treatment of cats with hyperthyroidism.

Daily dosage	Number of Cats (percent)			
Dose	Week 1	Week 4	Week 8	Week 12
15 mg	0	0	1 (5)	3 (15)
10 mg	20 (100)	18 (90)	14 (70)	12 (60)
5 mg	0	2 (10)	4 (20)	4 (20)
3 mg	0	0	1 (5)	1 (5)
n	20	20	20	20
Median dose (mg)	10	10	10	10
Mean dose (mg)	10	9.5	8.9	9.4

Table 3. Dose of oral carbimazole administered to cats in the study on the efficacy and safety of a novel lipophilic formulation of methimazole for the once daily transdermal treatment of cats with hyperthyroidism.

	Number of Cats (percent)			
Dose	Week 1	Week 4	Week 8	Week 12
7.5 mg & 5 mg q12h	0	0	3 (15)	1 (15)
5 mg q12h	20 (100)	17 (90)	10 (50)	10 (50)
5 mg q24h am & 5 mg qod pm	0	1 (5)	0	0
5 mg & 2.5 mg q12h	0	1 (5)	1 (5)	2 (10)
2.5 mg q12h	0	1 (5)	6 (30)	6 (30)
2.5 mg & 1.25 mg q12h	0	0	0	1 (5)
n	20	20	20	20
Median dose (mg)	10	10	10	10
Mean dose (mg)	10	9.6	9.1	8.1

Owner Compliance and Satisfaction

According to the questions asked to owners at each visit, all owners noticed a clinical improvement in the cats after treatment was instigated. Administering pills to cats in the oral carbimazole group proved to be a challenge with 7/20 (35%) owners admitting to missing doses or cats spitting doses out. Owners also reported cats becoming fractious when administering the pills. In the transdermal group, 100% of owners reported ease of application. Two owners reported missing a dose when the cat failed to return home when the dose of drug was due.

Long-term Follow-up

Fourteen owners of the cats in the transdermal methimazole group elected to continue treating their cats with the transdermal methimazole. A total of 54 TT4 concentrations were measured over a median follow-up period of 9 months (range 6–24 months). The median TT4 concentration was 2 μg/dL, mean 2.5 μg/dL (range 0.5–10.5 μg/dL). No adverse events were recorded.

Discussion

The results of this prospective study show that once daily dosing of transdermal methimazole in a novel lipophilic vehicle is safe and effective in the treatment of spontaneous hyperthyroidism in cats. Furthermore, in the 12-week trial, once daily transdermal methimazole was as effective as twice daily oral carbimazole. Owner compliance was high in the group treated with once daily transdermal methimazole. The transdermal application was found to have substantial advantages over oral medication as cats tolerated transdermal medication better than pills. Furthermore, the transdermal preparation required only once daily dosing to achieve disease control. These factors increased owner compliance and led to effective management of the hyperthyroidism.

Medical therapy is one of the 3 treatment options available for feline hyperthyroidism. [3–8] The transdermal application of drugs has become popular in feline medicine, as cats can be difficult to consistently medicate PO.[21–37] The vehicle carrier affects the absorption of drugs across the skin by having a primary role in determining the partition coefficient for the drug and can also alter the properties of the skin.[28] The correct vehicle is required for each drug for maximum transdermal penetration. As methimazole is a lipophilic drug, a lipophilic vehicle might be a better carrier[38] than the previously published methimazole PLO gel formulation. [24,25,29,39] Our study chose a lipophilic vehicle for transdermal delivery of methimazole. In addition to the formulation, other variables can affect

the transdermal delivery of drugs, including the skin blood flow, skin integrity, and hydration. Therefore, the site of application might change the rate of drug delivery, and this has been investigated in dogs, but not in cats.[43–45] However, previous studies of transdermal medications in cats have used the inner pinna [24,25,29,39] and this same site was selected for this study.

This 12-week study showed that once daily treatment with transdermal methimazole in a lipophilic vehicle was effective in decreasing TT4 concentrations into the reference range and led to clinical improvement (weight gain and reduced blood pressure) in all the treated cats. At the conclusion of the 12-week study, 14 of 20 owners of the cats in the transdermal group elected to continue treating their cats with transdermal methimazole. These cats continued to have good long-term control of their hyperthyroidism for up to 2 years, as demonstrated by TT4 concentrations within the reference range in the majority of the rechecks. Previous studies have shown that transdermal methimazole in PLO gel applied twice daily has short-term (4–8 weeks) efficacy in treating feline hyperthyroidism.[24,25] However, 1 study found this treatment to be less efficacious than oral treatment with methimazole, but resulted in fewer gastrointestinal adverse effects.[29] In contrast, we found once daily dosing with transdermal methimazole in a lipophilic vehicle to be as effective as oral carbimazole in reducing TT4 concentrations.

The starting dose of 10 mg once daily for transdermal methimazole and 5 mg twice daily for oral carbimazole was chosen for this study based on published studies.[13,25] The 2 starting daily doses are not equivalent. Carbimazole is a pro-drug of methimazole, with a molecular weight of 186 compared to a molecular weight of 114 for methimazole. Methimazole and carbimazole should be considered equivalent on a molar basis rather than a weight basis, and therefore in our study, 10 mg daily of carbimazole is equivalent to 6 mg daily of methimazole.[46] In the current study, the cats in the transdermal group received a higher mean dose of methimazole than the cats in the oral carbimazole group, and this may have contributed somewhat to the relative efficacy of the transdermal methimazole.

The plasma methimazole concentrations measured in this study correlated poorly with plasma TT4 concentrations in both treatment groups (Fig 2). Despite wide variation in the plasma methimazole concentrations achieved, clinical signs attributable to hyperthyroidism resolved in all treated cats. Previously, it has been shown that only low concentrations of methimazole in the plasma were reached when normal cats were dosed with methimazole via the transdermal route.[39] Pharmacokinetic studies on cats with hyperthyroidism and normal cats have shown methimazole to have a short half-life in the plasma (2.3 ± 0.4 hours for cats with hyperthyroidism and 4.7 ± 1.4 hours for normal cats).[17,42] Moreover, a recent study has shown that there is no relationship between the timing of blood sampling after oral methimazole and the TT4 concentration.[47] Therefore, because methimazole concentrates in the thyroid, plasma methimazole concentrations are unlikely to be correlated with plasma TT4 concentrations. The endpoint of successful treatment for these types of antithyroid drugs can be determined by their biologic effect, ie, the decrease in TT4 concentration and resolution of clinical signs rather than the plasma concentration of methimazole alone.

In this study, we collected samples 6–8 hours after carbimazole dosing and 18–20 hours after transdermal methimazole. These times were chosen based on the availability of the cats and owners, as the trough dose, ie, the time just before the next dose, could not be achieved. We found that TT4 concentrations remained suppressed for 18–20 hours after (Fig 1) treatment with transdermal methimazole, indicating that for this treatment, once daily application is sufficient. These results are similar to a recent study of healthy cats treated with once daily oral methimazole that showed significant suppression of thyroid hormone concentrations for 24 hours.[47]

Here, we demonstrate that transdermal methimazole in a lipophilic vehicle is safe to administer to cats. Previous studies on cats treated with methimazole have reported adverse effects of vomiting and diarrhea (15%), neutropenia (1.5%), pruritis or excoriation of the head (2.3%), and kidney disease (15–30%).[5,9,48,49] In the present study, 1 cat in the transdermal group developed acute vomiting, which resolved with a change of diet and 2nd cat in the oral group also developed vomiting which resolved with a reduction in dose. A single cat in the methimazole group developed neutropenia that resolved when treatment was stopped for 7 days. Six cats (15%) developed kidney disease during the trial: 3 in the transdermal group and 3 in the oral group. The rate of adverse effects observed during this trial was within the range reported in previous studies[5,9,48,49] of feline methimazole treatment suggesting that transdermal application of this lipophilic methimazole formulation is a safe treatment for cats.

Owner compliance and satisfaction were higher in the transdermal group than in the oral carbimazole group. Identifying barriers to owner compliance is a way of improving adherence to a medical therapy, and time constraints and convenience are 2 barriers that have been identified.[50] Logically, a medication that is applied once daily is more convenient to owners than twice daily medications. Transdermal medications are also more convenient to owners that have difficulty in administering pills to their cats. When medically treating cats with hyperthyroidism, consistent adherence and compliance are important, as the disease is only controlled when the drug is administered at the recommended dosing interval. There are, however, disadvantages of transdermal drug delivery. Cutaneous irritation can occur[28] and potentially, there is increased or inadvertent drug exposure to clients or other animals, which does necessitate the use of nonpermeable gloves when administering the drug.[32]

In conclusion, treatment of feline hyperthyroidism with once daily transdermal methimazole in a novel lipophilic vehicle, improved clinical signs, suppressed TT4, and was well tolerated by cats. In addition, owner compliance was higher with once-daily medication applied to the skin than twice-daily medication dosed PO.

Footnotes

[a] Norvasc, Pfizer New Zealand Ltd, Auckland, New Zealand
[b] Neo-Mercazole, AFT Pharmaceuticals, Auckland, New Zealand
[c] Advia 120 Automated hematalogy analyzer, Bayer, Tarrytown, NY
[d] Hitachi 911, Roche Diagnostics, Tokyo, Japan
[e] Clinitex 50, Bayer, using Siemens multistix 10 Los Angeles, CA
[f] Immulite, Siemens
[g] The R Foundation for Statistical Computing, Vienna, Austria
[h] Clavulox palatable drops, Pfizer New Zealand Ltd
[i] Hill's ZD Hill's Pet Nutrition, Inc, Topeka, KS

Acknowledgments

The authors thank the veterinary clinics (Central City Vets, Cahill's Animal Hospital, Terrace End Veterinary Clinic, Totally Vets, and Vet Services Dannevirke) that helped recruit cases and referred these cases into the Veterinary Teaching Hospital.

Grant support: This study was funded by a grant from Bomac Laboratories Ltd.

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Appendix

Table A1. In the study on the efficacy and safety of a novel lipophilic formulation of methimazole for the once daily transdermal treatment of cats with hyperthyroidism, owners of the enrolled cats were asked to complete a questionnaire when cats were evaluated at 0, 1, 4, 8, and 12 weeks.

Since the last recheck, have you noticed your cat doing any of the following	
Vomiting	Yes/No
	If Yes how often multiple times a day/daily/few times a week/weekly
Diarrhea	Yes/No
	If Yes how often multiple times a day/daily/few times a week/weekly
Scratching at the ear	Yes/No
	If Yes how often multiple times a day/daily/few times a week/weekly
Not eating	Yes/No
	If Yes how often multiple times a day/daily/few times a week/weekly
Eating has increased	Yes/No
	If Yes how often multiple times a day/daily/few times a week/weekly
Eating has been stable	Yes/No
Lost any weight	Yes/No
Any coat changes	Yes/No
Please describe any other abnormalities:	