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The efficacy of a unique topical dose of methimazole in cats – A case presentation

Eficacitatea unei doze topice unice de metimazol la pisici – O prezentare de caz

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Abstract

Methimazole or thiamazole is the most commonly used remedy in the medical management of hyperthyroidism, an endocrine disorder with growing prevalence, particularly in geriatric feline patients. Unfortunately, veterinarians have little, or most often, no access to the transdermal conditionings. The novelty of this research is that very few. transdermal formulations that include methimazole are studied yet in the veterinary field, and most often, the efficacy of methimazole is studied using pluronic lecithin organogel or lipophilic formulations as a vehicle in healthy or hyperthyroid cats. In this aim, our study followed a formulation of topical methimazole that includes a human base cream as a vehicle. Five healthy cats were included in this study and received 0.1 mL cream containing 10 mg methimazole over 15 days. The ointment was applied to the hairless portions of the inner pinna and: the body weight, hematological, biochemical parameters, the adverse effects, and total thyroxin serum concentration were monitored on day 0 and day 16. Topical reactions were observed after treatment, on day 14, after 15 days of topical methimazole application. Thyroxin serum concentration was significantly lower compared to the concentrations seen on day 0, allowing us to conclude that, the incorporation of methimazole in a dermatological cream base induces, at the same dose of 10 mg × 0.1 mL^{-1}, a significant change in total thyroxin levels, changes comparable to those acquired by other authors using PLO or lipophilic gel.

Rezumat

Metimazolul sau tiamazolul este cel mai frecvent utilizat remediu în managementul medical al hipertiroidismului, o tulburare endocrină cu prevalență în creștere, în special la pacienții geriatrici feline. Din păcate, medicii veterinari au acces redus sau cel mai adesea deloc la condiționările transdermice. Noutatea acestei cercetări este că foarte puține. Formulările transdermice care includ metimazol sunt încă studiate în domeniul veterinar și, cel mai adesea, eficacitatea metimazolului este studiată folosind lecitină pluronică organogel sau formulări lipofile ca vehicul la pisicile sănătoase sau hipertiroidiene. În acest scop, studiul nostru a urmat o formulă de metimazol topic care include o cremă de bază umană ca vehicul. Cinci pisici sănătoase au fost incluse în acest studiu și au primit 0,1 ml cremă care conține 10 mg metimazol timp de 15 zile. Unguentul a fost aplicat pe porțiunile lipsite de păr ale țevii interioare și: au fost monitorizate greutatea corporală, parametrii hematologici, biochimici, efectele adverse și concentrația totală de tiroxină în ser în ziua 0 și ziua 16. Reacțiile topice au fost observate după tratament, în ziua 14, după 15 zile de aplicare topică a metimazolului. Concentrația serică de tiroxină a fost semnificativ mai mică comparativ cu concentrațiile observate în ziua 0, permițându-ne să concluzionam că, încorporarea metimazolului într-o bază de cremă dermatologică induce, la aceeași doză de 10 mg × 0,1 mL-1, o modificare semnificativă a totalului nivelurile de tiroxină, modificări comparabile cu cele dobândite de alți autori folosind PLO sau gel lipofil.

1. Introduction

Feline hyperthyroidism is a syndrome associated with disproportionate thyroid hormone production, an endocrine disorder with growing prevalence, particularly in geriatric feline patients [1].

Methimazole or thiamazole is the most commonly used remedy in the medical management of hyperthyroidism. Employing this medication has the advantage of being a cheap and high efficacy treatment that can be dispensed, for a long time, even for the animal's whole life [2,3].

Methimazole, a thioamide-based antithyroid substance, is used for its capacity to interfere with thyroid hormone synthesis by blocking the activity of thyroid peroxidase (TPO), with a role in the tyrosine residue iodination. In this way, the monoiodotyrosine (MIT) and diiodotyrosine (DIT) coupling will be impacted, deterring the formation of thyroxine (T4) and triiodothyronine (T3) [4].

Methimazole accumulates in the thyroid gland, but it has no effect on circulating or assembled thyroid hormones [5].

Orally dispensed, the efficacy of methimazole is greater than 90%, and depending on the existence of the concurrent diseases, it can be administered commencing with small doses ranging from 2.5 mg to 5.0 mg / 12 h [6].

The authors observed that in the first 2-4 weeks of treatment, up to 20% of cats treated with methimazole experienced various adverse effects such as vomiting, anorexia, and lethargy. These side effects can be transient or persist until the methimazole's administration ceases.

To eliminate adverse effects, associated with the oral administration, some researchers tried to compound a topical form of methimazole using pluronic lecithin organogel (PLO), a new transdermal drug delivery system that enhances the transport of drugs across and into the skin [7-9].

The transdermal route has its advantages: the drug avoids gastrointestinal absorption and first-pass metabolism, which represents a good alternative when oral medication is inconvenient.

Despite the multiple benefits, skin irritation or dermatitis can occur due to the excipient, the absorption of the drug, being limited by the skin [10, 11].

Methimazole administered orally in cats comes with the risk of side effects that may result in discontinuation of treatment with a negative influence on the cat's health. Compared to the oral way, one benefit of the transdermal way of methimazole is the ease of administration.

The transdermal administration decreases or even annihilates all oral way side effects, and this is why recent studies with methimazole transdermal formulations are completed. In general, the pharmacokinetic properties of methimazole via transdermal applications have been studied, using two types of vehicles that include PLO and a new lipophilic formulation.

Based on their effects, we know that methimazole in the dose of 10 mg/day applied to the inner pinna of the cat can reach systemic circulation reducing thyroid hormone synthesis [12-15].

Unfortunately, in Romania, but likewise in other countries, veterinarians have little, or most often, no access to the transdermal conditionings. Because of these drawbacks, we have decided to make an equivalent authentic drug formulation that can support veterinarians.

Since, in this subject, information is lacking, our *ab initio* study emerged as a necessity, and attempt to determine the clinical efficacy of the new conceived transdermal methimazole cream, laid on the inner pinna of healthy cats (to avoid large values fluctuation as in ill cats), to a total dose of 10 mg × day^{-1}.

We followed the effects over the total serum thyroxin concentration, comparing results obtained before and after the transdermal methimazole administration in cats.

2. Materials and Methods

2.1. Animals

To conduct this study, we established that solely healthy cats should participate because

cats influenced by hyperthyroidism usually have multiple associated disorders, such as kidney failure, heart failure, or diabetes, which demand the administration of several drugs at one time.

Hence healthful cats have provided us the uncontroversial possibility to investigate methimazole's adverse effects. So, we observed the alteration of hematological and biochemical parameters such as ALT, ALP, and Thyroxin, which modifies following oral methimazole administration.

Five healthy and neutered cats, provided from the same household, were included in this study. Cats were regular patients of the Veterinary clinic from Veterinary Faculty Timisoara. All cats were considered healthy at the beginning of the study, based on the results obtained from the physical exam, biochemical panel, and complete blood count test.

To execute this study, no special approval was needed, being respected the guidelines of the Ethical Committee of the Banat University of Agricultural Science and Veterinary Clinics from Timisoara, for the examinations of the health of animals, the sole owner being fully informed about any risks associated with the blood sampling techniques, and that the investigation will be disseminated, and he consented to the therapeutic protocol.

Before the study initiation, cats were dewormed and was verified the vaccine status for each. The age of the cats was between two (*n*: 2) and three years (*n*: 3), with an average weight between 3.8 and 6.6 kg.

The cats were fed with a dry diet and canned food (Sanabelle, Bosch Tiernahrung GmbH, Germany), and dry meals and water were provided ad libitum daily.

2.2. Medicinal recipe

The *active substance* methimazole, used in the formulation was obtained from Sigma-Aldrich Co. LLC, (Methimazole M8506 ≥99%, Lot: WXBC1539V).

The *cream base* (Mayam, Elemental RO) employed as a complex excipient is an amphiphilic cream base including aqua, caprylic/capric triglyceride, propylene glycol, hydrogenated lecithin, glycerin, *Butyrospermum parkii* butter, C12-16 alcohols, palmitic acid, Squalane, Ceramide NP. The final product consisted of simply combining 100 mg of methimazole (as a fine powder) with a 1 mL cream base, subsequently stored at room temperature in insulin syringes at a final concentration of 100 mg × mL^{-1}.

2.3. Clinical study

The study period was of 15 days. The cream was spread, as 0.1 mL (10 mg active substance) from day one, once per day, for 15 successive days, on the ear's inner pinna. After a preliminary cleaning of the inner pinna with warm water, the methimazole cream has applied to the hairless portion of the inner pinna, in a dose of 0.1 mL, every day, around the same hour (19.00 hours).

For application were used disposable gloves, using alternate ears after each dose. The time needed to absorb the cream was short, 30-40 seconds.

Depending on the behavioral state of each cat, the subjects were monitored one hour after each treatment.

Blood sampling from the jugular vein was accomplished on day 0, and at the end of the experiment, on day 16. Before the blood sampling, the food administration stopped for 12 hours.

The blood specimens were collected in hematology vacutainer tubes, using EDTA as an anticoagulant.

The blood samples for dosing total thyroxine (TT4), alkaline phosphatase (ALP), and alanine aminotransferase (ALT), were collected in serum separator tubes (BD Vacutainer SST II, Advance) and centrifuged at 1000 rpm for 20 minutes, followed by a 30-minute rest then, blood samples, were sent to a nationally accredited laboratory (Synevovet, Bucharest, RO) for paraclinical analysis.

2.4. Statistical analysis

The statistical interpretation of the obtained results was performed using a parametric method, One-Way ANOVA considering that the differences are statistically provided when $p < 0.05$, or less.

The applied software was Graph Pad Prism 6.0 for Windows. (Graph Pad Software, San Diego, USA).

3. Results

3.1. General observations

Over 15 days of treatment, no behavioral changes or other health alterations in any subject were ascertained, and food and water consumption were similar to pre-experimental monitoring.

3.2. Biochemical panel

At the end of the experimental period, mean values of ALT and ALP did not show significant changes (p <0.05) compared to values recorded at the beginning of the experiment (Table 1).

The mean TT4 concentration on only 16 (TT4 = 2.85 μg × dL^{-1}) was significantly lower (**p< 0.05) than the mean concentration on day 0 (TT4 = 1.22 μg × dL^{-1}) in all cats treated with 10 mg of transdermal methimazole (Table 2 and figure 1).

Table 1.
Average values of biochemical parameters determined before and after methimazole transdermal administration

Parameter	Period	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5
ALT (UI × L^{-1})	before	56.00	63.00	88.00	70.00	56.00
	after	47.00	73.00	66.00	48.00	45.00
ALP (UI × L^{-1})	before	26.28	11.09	21.03	0.00	26.63
	after	19.21	8.21	14.22	6.37	14.64
TT4 (μg × d^{-1})	before	2.65	2.53	2.68	4.18	2.21
	after	2.00	1.16	0.90	0.90	1.17

Legend: ALT = alanine aminotransferase; ALP = alkaline phosphatase; TT4 = total serum thyroxin

Table 2
Statistical interpretation of biochemical parameters in cats before and after treatment with methimazole

Descriptives

Parameter		No.	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.
						Lower Bound	Upper Bound		
ALT	Before	5	66.600	13.296	5.946	50.0901	83.109	56.00	88.00
	After	5	55.800	12.794	5.721	39.913	71.686	45.00	73.00
ALP	Before	5	17.006	11.391	5.094	2.862	31.149	.00	26.63
	After	5	12.530	5.209	2.329	6.062	18.997	6.37	19.21
TT4	Before	5	2.850	.766	.342	1.898	3.801	2.21	4.18
	After	5	1.226	.452	.202	.664	1.787	.90	2.00

	Parameter		*Sum of Squares*	*df*	*Mean Square*	*F*	*Sig.*
ALT	Between Groups		291.600	1	291.600	1.713	.227
	Within Groups		1362.000	8	170.250		
		Total	**1653.60**	**9**			
ALP	Between Groups		50.086	1	50.086	.638	.447
	Within Groups		627.563	8	78.445		
		Total	**677.649**	**9**			
TT4	Between Groups		6.593	1	6.593	16.645	.004*
	Within Groups		3.169	8	.396		
		Total	**9.762**	**9**			

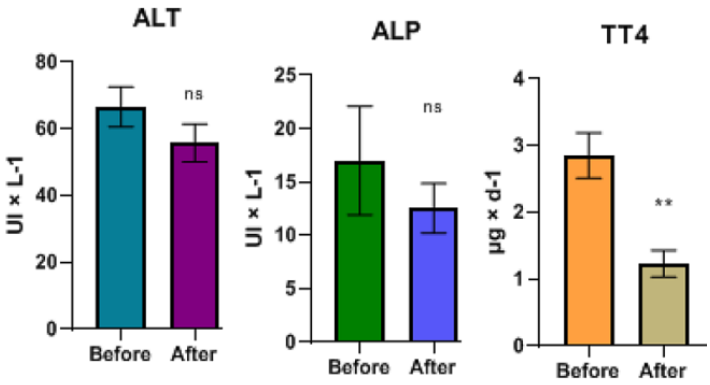

Figure 1. Statistical interpretation of biochemical parameters before and after methimazole treatment (where: **p <0.05 high statistically significant)

3.3. Hematological parameter

Comparing hematological values from day 0 to day 16, there were no statistically significant changes except for the percentage of reticulocytes whose statistical significance (**p <0.05) and value were lower after treatment (Table 3).

Table 3.
Hematological parameters in cats before and after treatment with methimazole

Parameter		Cat 1	Cat 2	Cat 3	Cat 4	Cat 5
WBC (K × µL^{-1})	Before	4.84	7.90	8.94	5.77	6.35
	After	5.20	8.23	6.76	7.32	2.86
RBC (M × µL^{-1})	Before	10.90	10.36	9.29	9.10	9.61
	After	11.06	10.55	8.40	8.85	8.81
HGB (g × dL^{-1})	Before	16.00	15.00	15.20	13.90	14.50
	After	15.70	14.80	13.20	13.30	13.20
HCT (%)	Before	44.60	41.90	42.30	37.00	42.50
	After	44.30	42.90	39.30	37.20	38.60
MCV (fL)	Before	41.00	40.50	45.50	40.70	44.20
	After	40.00	40.60	46.80	42.00	43.80
MCH (pg)	Before	14.70	14.40	16.30	15.30	15.10
	After	14.20	14.00	15.80	15.00	15.00
MCHC (g × dL^{-1})	Before	35.80	35.70	35.90	37.50	34.10
	After	35.50	34.50	33.70	35.80	34.20
RDW (%)	Before	16.10	15.60	15.00	15.00	14.40
	After	15.80	15.20	14.20	13.90	13.50
PLT (K × µL^{-1})	Before	296.00	229.00	163.00	230.00	241.00
	After	258.00	241.00	121.00	339.00	253.00
MPV (fL)	Before	19.00	18.60	17.10	15.30	15.60
	After	19.30	17.50	18.30	14.80	16.30
Retic (%)	Before	0.17	0.16	0.18	0.27	0.14
	After	0.14	0.08	0.14	0.08	0.10
Retic (K × µL^{-1})	Before	18.20	16.70	16.40	24.50	13.60
	After	15.40	8.50	11.90	7.50	8.60
N (%)	Before	51.90	47.70	44.80	42.50	56.20
	After	49.30	69.30	62.10	60.90	56.00
L (%)	Before	44.80	42.50	48.20	48.70	36.80
	After	44.60	25.30	34.50	30.30	41.40
M (%)	Before	1.10	1.40	1.60	2.00	1.90
	After	2.70	1.20	1.90	1.40	2.60
E (%)	Before	2.00	8.20	5.30	6.60	4.90

	After	3.20	3.80	1.40	7.20	0.00
B (%)	Before	0.10	0.20	0.10	0.20	0.10
	After	0.10	0.30	0.10	0.20	0.00
N (K × μL^{-1})	Before	2.51	3.77	4.00	2.45	3.57
	After	2.57	5.70	4.19	4.45	1.60
L (K × μL^{-1})	Before	2.17	3.36	4.31	2.81	2.34
	After	2.32	2.08	2.33	2.22	1.18
M (K × μL^{-1})	Before	0.05	0.11	0.14	0.11	0.12
	After	0.14	0.10	0.13	0.10	0.07
E (K × μL^{-1})	Before	0.10	0.64	0.48	0.38	0.31
	After	0.17	0.31	0.10	0.53	0.00
B (K × μL^{-1})	Before	0.01	0.02	0.01	0.01	0.01
	After	0.00	0.03	0.01	0.01	0.00

Legend: WBC= leukocytes; RBC= red blood cell count; HGB = hemoglobin; HCT = hematocrit; MCV = mean red blood cell volume; MCH = average volume of hemoglobin; MCHC = mean concentration of hemoglobin; RDW = red cell distribution width; PLT = platelets; MPV = mean red blood cell volume; Retic = reticulocytes; N = neutrophils. L = lymphocytes; M = monocytes; E = eosinophils; B = basophils.

3.4. Adverse effects examination

Adverse effects observed were mild and in the form of eczema, found in two of the five cats examined: in cat no. 3, a 0.5 cm reddish excoriation on the inner pinna (Fig. 2A), and cat no. 5, on the temples zone, a development similar to wet eczema with the size of 1 cm (Fig.2 B and C).

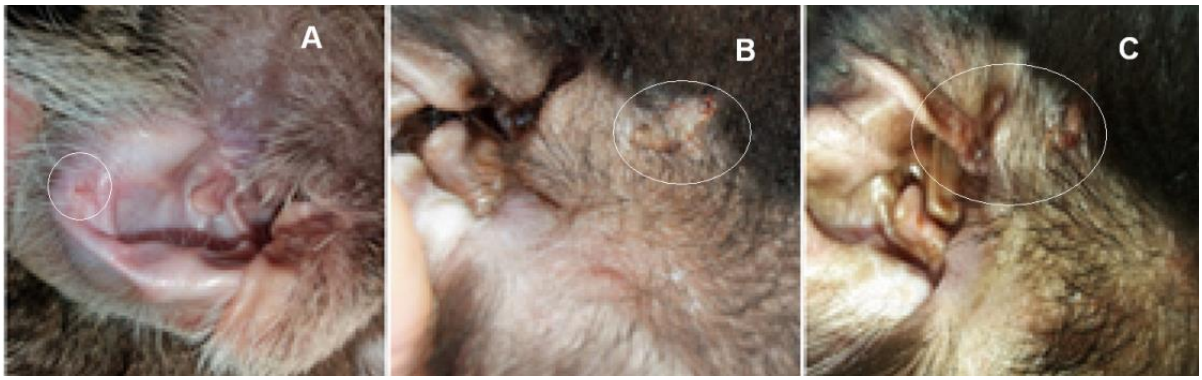

Figure 2. Cutaneous dermatitis resulting from topical application of methimazole: reddish and irritated skin on the right ear in cat 3 (A); eczema on the right temple of cat 5 (B and C)

4. Discussion

Because of the deficient choices, the pharmacotherapy of hyperthyroidism in Romania is based yet on the inhibitory influence on the synthesis of thyroid hormones of thioamides, like methimazole and carbimazole. Methimazole remains an efficient structure used as the number one therapy in feline hyperthyroidism [16].

Due to the difficulty in administering a pill to a cat, the veterinarians are trying to formulate and use topical formulations of methimazole to allow an easier administration of the medication and the side effects decrease. The use of such a system offers a new treatment option valued by having the advantage of diminishing or eliminating the adverse effects encountered following the oral administration of methimazole [17].

Although there are currently a limited number of studies in which methimazole via a PLO gel was applied. Its efficacy has favored its presence on the international market.

The existence and difficulty of purchasing this type of product are at the basis of this study which attempted to incorporate methimazole and obtain a new topical formulation having as

a vehicle an easily obtained cream base by the therapist. Previous studies have used the pluronic lecithin gel (PLO gel) as an excipient consisting of two phases, one aqueous and one organic.

It is an emulsion whose aqueous composition is concreted from Pluronic F 127 20-30% to which added the lipid phase represented to the same extent by lecithin, either as isopropyl palmitate or isopropyl myristate [18, 19].

Hoffman et al. [2] documented the bioavailability of methimazole in PLO gel and concluded that, following transdermal administration, the bioavailability of methimazole was significantly reduced compared to oral bioavailability.

Thirteen years later, the percutaneous absorption of methimazole was also studied by Hill et al. [12] using two types of vehicles, one based on PLO gel and the other in lipophilic form. The authors concluded that both formulations favored the passage of methimazole through the auricular pavement, but the lipophilic formula is much more meaningful and effective.

Starting from the same principle, in the present study, we tried to replace that type of PLO gel with a natural cream, incorporating methimazole at a concentration of 100 mg × 1 mL^{-1} and administering at a dose of 10 mg/cat/day for 16 days. According to the literature, the application of PLO gel (0.1 mL) on the inner pinna should be followed by the excess gel removal at 30-120 minutes after application [19,20].

Unlike this feature of the PLO gel, in our case, after application, cream (0.1 mL) was absorbed rapidly. Since this treatment also needs contention, and in our case, two out of five cats were more challenging to maintain, we have seen that the topical methimazole application is recommendable vs. the oral administration, thus requiring a more demanding contention.

The efficacy of the conceived cream was confirmed by detecting significant changes (p <0.05) by comparing the TT4 values at the beginning of treatment (TT4 = 2.85 µg × dL^{-1}) with the end-of-treatment values (TT4 = 1.22 µg × dL^{-1}).

In a similar study, Hill et al. [12], using a lipophilic formulation as a vehicle for methimazole, observed no significant changes in TT4 value after methimazole of 5 mg/day or even after, increasing the dose to 10 mg/day for 7 days.

However, another study conducted by the same author, now over 12 weeks, had better outcomes, ending with the induction of euthyroidism in hyperthyroid cats and, compared with the oral way administration, all owners preferred transdermal administration [13].

In another study, Sartor et al. [8], obtained comparable results, both with topical and oral methimazole therapy, by reducing the serum TT4 concentration in the first 2 weeks.

Although there were no significant changes in biochemical parameters, we observed that serum ALT and ALP values on day 16 decreased (ALP = 17.00; ALT = 66.60), compared to serum values on day 16 (ALP = 12, 53; ALT = 55.80). Similar changes have also been observed in rats, concluding that methimazole reduces the enzymatic activity of ALT and ALP [21].

Confronting results in humans, the administration of methimazole has increased the enzymatic activity of ALT [1,16].

Four of the five cats were found to have mild lymphocytopenia, but not statistically significant (p <0.05). Nambiar et al. found the presence of lymphocytopenia and also reticulocytopenia in rats [21]. Similar to Nambiar's observations, along with lymphocytopenia, rea duction in reticulocyte counts was evident in the cats in this study, dropping from a peak of 0.27 K × $\mu L^{-=1}$ to 0.08 K × μL^{-1} [21].

Data from this study are in contradiction with lymphocytosis presented by other authors who considered that lymphocytosis is an adverse effect of oral administration of Methimazole and can be found in 15% of all treated hyperthyroid cats [14, 17].

From literature, the gastrointestinal side effects are emerging in the first 4 weeks of treatment, being translated by vomiting (11%),

anorexia (11%), or even lethargy (9%) and are typically witnessed following oral administration of methimazole, signs being transient and disappearing after discontinuation of treatment. In contrast to oral administration, transdermal therapy with methimazole favors the severe reduction of these side effects [14].

In the current study, during 15 days of topically applied methimazole, no gastrointestinal side effects were observed in the treated cats. Hoffmann et al. [4] also observed that methimazole topical administration was connected with adverse effects elimination in the case of cats exhibiting gastrointestinal signs, consecutive the oral therapy with methimazole.

The studies are esteemed that, facial excoriations have a prevalence of 2% in cats treated with methimazole and occur within the first 4-8 weeks of treatment. Although it disappears following glucocorticoid therapy, methimazole administration needs to be discontinued [17].

In our case, the occurrence of mild excoriations was present in two of five cats, and these were observed on day 14 of the treatment, missing after one week from discontinuation of methimazole treatment.

The mild erythema of the inner pinna was also reported by Lecuyer et al. [20] in a study that evaluated the efficacy of methimazole in PLO gel at a daily concentration of 0.5 mg / 0.1 mL, the existence of pruritus, and mild erythema, following topical methimazole administration was also confirmed by Wu's study [22].

5. Conclusions

Based on the results, we considered that methimazole incorporation in a dermatological cream base induces, at the same dose of 10 mg × 0.1 mL^{-1} significant change in total thyroxin levels, changes comparable to those achieved by other authors using PLO or lipophilic gels.

The conceived topical conditioning is a simple, practical, and easy-to-use alternative that may perhaps be considered by vet practitioners.

All authors have read and agreed to the published version of the manuscript.

Conflict of interest statement: The authors declare no conflict of interest.

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