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Original Article

Evaluation of the Efficacy and Safety of an Imidacloprid 10%/Moxidectin 1% Spot-on Formulation (Advocate®, Advantage® Multi) in Cats Naturally Infected with *Capillaria aerophila*

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Abstract

The parasitic nematode *Capillaria (C.) aerophila* affects the respiratory system of domestic and wild animals and, albeit rarely, human beings. In cats the infection may be subclinical, or present as chronic bronchitis with various respiratory clinical signs. In Europe there is no licensed product for the treatment of pet capillariosis. The present study aimed to deliver further evidence of the efficacy and safety of a spot-on formulation containing moxidectin 1% (w/v) and imidacloprid 10% (w/v) (Advocate®, Advantage® Multi, Bayer) in the treatment of *C. aerophila* infection in cats when administered once at the approved dose (one pipette 0.4 ml for cats weighing 1–4 kg, one pipette 0.8 ml for cats weighing 4–8 kg). Efficacy was tested on days 7±1 and 11±1 following treatment on day 0 and compared to pre-treatment faecal egg counts on days -6±2 and -2±2. Overall, 41 cats were enrolled in two groups: G1, treated with Advocate® (n=20 cats) and G2, left untreated (n=21 cats). All G1 cats were negative for *C. aerophila* faecal egg output at the post-treatment evaluation (efficacy: 100%) while all G2 cats were persistently infested with an average of 195.2 EPG. Differences in mean EPG values were statistically significant ($p < 0.001$). Of the eleven G1 cats that showed respiratory signs at pre-treatment enrolment, nine fully recovered after the administration of Advocate®. No adverse events occurred in treated cats. This trial confirmed that Advocate®

is safe and effective in the treatment of feline lung capillariosis in naturally infected cats.

Introduction

Capillaria (C.) aerophila (syn. *Eucoleus aerophilus*) is a parasitic nematode that affects the respiratory tract of dogs, cats, wild carnivores (Canidae, Mustelidae, Felidae) and, occasionally, humans (Lalosević et al. 2008; Di Cesare et al. 2014a). The adult parasites are whitish, slender and filamentous nematodes, measuring ~20–40 mm in length and ~60–180 µm in width and inhabiting the epithelium of the host's trachea and bronchi, where females produce non-embryonated ova (Bowman et al. 2002, Conboy et al. 2009). The eggs are coughed up and swallowed by the host and then shed in the faeces. These eggs have a net-like outer shell, measure ~60–65 x ~25–40 µm, have a typical morphology (Fig. 1) and present asymmetry of bipolar plugs (Traversa et al. 2011). Infective larvae develop into eggs in the environment, where they are very resistant. Earthworms have been hypothesized to act as a facultative or paratenic intermediate host. Cats therefore become infected by ingesting larvated eggs from the soil and/or an infected earthworm (Bowman et al. 2002).

Capillaria aerophila is common in cats in several European countries, e.g. Denmark, Italy, Romania and Portugal (Mircean et al. 2010; Waap et al. 2014; Di Cesare et al. 2015a; Hansen et al. 2017). The infection in cats may be subclinical, although the parasite is capable of inducing chronic bronchitis with various clinical signs (e.g. bronchovesicular sounds, sneezing, wheezing, and chronic dry cough). Bronchopneumonia, productive cough and respiratory failure may occur when the parasite burden is heavy and/or if bacterial complications occur (Holmes and Kelly 1973; Bowman et al. 2002; Traversa et al. 2009a).

Although *C. aerophila* is apparently spreading in pets in Europe, and despite its pathogenic role in cats and the existence of a zoonotic potential, this

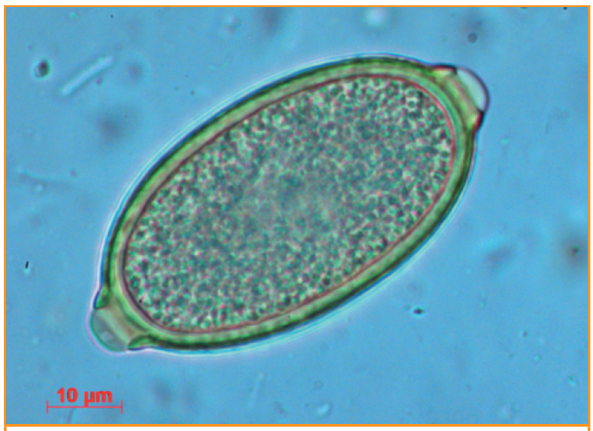

Fig. 1 Egg of *Capillaria aerophila*

is an underestimated parasite and no commercial products are licensed in Europe for treatment of the infection (Traversa and Di Cesare 2016; Traversa et al. 2010).

Advocate® (Bayer) is a spot-on formulation containing the macrocyclic lactone endectocide moxidectin 1% (w/v) and the neonicotinoid insecticide imidacloprid 10% (w/v) that is currently approved in Europe for the treatment of a wide range of ectoparasites and endoparasites of cats.

A Good Clinical Practice (GCP) study carried out from 2009–2011 demonstrated the efficacy and safety of Advocate® in the treatment of cat capillariosis (Traversa et al. 2012). This article describes a second GCP trial that has been performed to further evaluate the therapeutic efficacy and safety of Advocate® in cats naturally infected with *C. aerophila*.

Materials and methods

Study design

The study was a controlled, randomized, multicentric field study conducted according to European and Italian regulatory requirements and in compliance with the following documents:

- Buone pratiche di sperimentazione clinica dei medicinali veterinari sugli animali – Gazzetta

ufficiale Della Repubblica Italiana, Ministero Della Salute n. 291 del 12/11/2011.
- VICH GL9 - GCP, "Good Clinical Practice" (CVMP, June 2000).
- CVMP/816/00-Final: Guidelines of Statistic Principles in Veterinary Clinical Trials (CVMP December 2001)
- CVMP/VICH 832/99-Final: Efficacy requirements for anthelmintics: overall guidelines (VICH GL7, November 2000)
- CVMP/VICH 835/99-Final: Efficacy of anthelmintics: specific recommendations for felines (VICH GL19, July 2001)
- EMA/CVMP/EWP/81976/2010 – Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)

Approval to conduct the study was obtained beforehand from the regulatory authority (Italian Health Ministry, Authorization No. 0009898 – 15/04/2015-DGSAF-COD_UO-P) and animals were included in the study pending written informed consent from the owner.
Three veterinary practices (Sites A-C) located in central Italy (see acknowledgements) participated in the study that was carried out from May to November 2015.
After pre-inclusion screening based on a qualitative faecal examination, positive animals underwent two pre-treatment quantitative copromicroscopic examinations on days -6±2 and -2±2, a clinical examination and treatment with the anthelmintic on day 0 and two post-treatment quantitative copromicroscopic examinations on days 7±1 and 11±1.

Pre-inclusion screening

On days -11±2 and -7±2 a preliminary screening based on a qualitative assessment of the faecal *C. aerophila* egg output by the routine flotation method (Sloss et al. 1994) was conducted.
Cats that were positive for *C. aerophila* eggs (Fig. 1) at least at one of the two analyses were considered as candidates for enrolment in the study. Eggs of *C. aerophila* were identified using morphologic and morphometric features (i.e. size, shape, plug morphology and appearance of the egg shell) (Traversa et al. 2011). Of the 330 screened cats, 41 (12.4%, 41/330) of them were infected by *C. aerophila*. Specifically, 16, 20 and 5 cats come from site A (12.4%, 16/129), B (20.6%, 20/97) and C (4.8%, 5/104), respectively.
All cats with positive results for *C. aerophila* at screening were further evaluated by inclusion and exclusion criteria for enrolment in the study.

Inclusion and exclusion criteria

Animals that scored positive for eggs of *C. aerophila* at the pre-inclusion screening were subjected to physical examination and quantitative copromicroscopic examinations using a McMaster method (Sloss et al. 1994) at days -6±2 and -2±2 to evaluate the pretreatment values of egg per gram of faeces (EPG). Cats satisfying the following criteria were included in the study

- Cats for which the owner provided the written Owner Consent Form;
- Cats with satisfactory general health conditions at physical examination;
- Cats over 9 weeks of age and ≥1 kg in weight, in accordance with the label of Advocate®;
- Cats not treated in the 30 days previous the inclusion and not intended to be treated in the 20 days following inclusion with antiparasitic products with suspected/confirmed activity against *C. aerophila*;
- Cats without lesions in the area in which the formulation is applied;
- Cats for which none of the restrictions of the product label was applicable.

Cats showing severe clinical signs of *C. aerophila* infection and for which participation in the study could potentially compromise their health were not suitable for inclusion in the study on an animal welfare base.

Table 1 Weights of cats enrolled in G1, dosage of Advocate® (imidacloprid 10 % / moxidectin 1 %) applied and doses of moxidectin administered actually in terms of mg/kg body weight (b.w.).

Cat ID	Weight (kg)	Dosage applied imidacloprid (mg)	Dosage applied moxidectin (mg)	moxidectin (mg/kg b.w.)
AB001	2.2	40	4	1.82
AD001	4.0	40	4	1.00
AE001	4.8	80	8	1.67
AE002	3.7	40	4	1.08
AH001	3.0	40	4	1.33
AH002	3.2	40	4	1.25
AJ001	1.2	40	4	3.33
AJ002	3.7	40	4	1.08
BA001	3.6	40	4	1.11
BA002	5.2	80	8	1.54
BA003	3.8	40	4	1.05
BC001	4.8	80	8	1.67
BE001	5.2	80	8	1.54
BG001	4.5	80	8	1.78
BG002	4.4	80	8	1.82
BG003	3.6	40	4	1.11
BI001	4.4	80	8	1.82
BI002	3.2	40	4	1.25
CA001	1.1	40	4	3.64
CC001	6.3	80	8	1.27

Anthelmintic treatment

On day 0 cats were clinically examined and randomly assigned to one of the two groups G1 (n = 20 cats) and G2 (n = 21 cats). In order to avoid contact between treated and untreated cats, all animals living in the same household were allocated to the same treatment group.

Cats assigned to G1 received a single administration of Advocate® according to body weight and label instructions (Table 1), while cats in G2 were left untreated and received a rescue dose of Advocate® after completion of the study.

Post treatment evaluation

Faecal samples collected on days 7 ± 1 and 11 ± 1 were subjected to two quantitative McMaster examinations and cats were again physically examined.

The efficacy of treatment was evaluated based on the Faecal Egg Count Reduction (FECR) versus the baseline EPG for each group and was calculated as follows:

$$\text{FECR \%} = \frac{\text{pre-treatment mean EPG} - \text{post-treatment mean EPG}}{\text{pre-treatment mean EPG}} \times 100$$

Table 2 Mean egg per gram of faeces (EPG) count values at different times in the study. The highest value from the two egg counts performed in the pre-treatment assessments [on days -6 ± 2 and on days -2 ± 2] were used as the baseline value for efficacy calculation. The highest value from the egg counts performed post-treatment [on days 7 ± 1 on days 11 ± 1] was used as the post-treatment value for efficacy calculation.
SD: standard deviation; SE: standard error; CI: confidence interval.

	Group	N	Mean EPG	SD	SE	95 % CI for Mean		Min	Max
						Lower bound	Upper bound		
Days -6 (±2)	1	20	132.5	106.7	23.86	82.56	182.44	0	350
	2	21	195.2	209.1	45.63	100.05	290.42	50	1050
			P=0.2371						
Days -2 (±2)	1	20	152.5	137.2	30.667	88.313	216.69	0	550
	2	21	154.8	223.0	48.661	53.256	256.27	0	1050
			P=0.9692						
Baseline	1	20	180.0	135.1	30.22	116.75	243.25	50	550
	2	21	223.8	202.3	44.13	131.75	315.87	50	1050
			P=0.4221						
Days 7 (±1)	1	20	0	0	0	0	0	0	0
	2	21	181.0	188.7	41.18	95.04	266.86	50	950
			P=0.0001						
Days 11 (±1)	1	20	0	0	0	0	0	0	0
	2	21	164.0	200.7	43.8	72.92	255.65	0	1000
			P=0.0007						
Post-treatment	1	20	0	0	0	0	0	0	0
	2	21	195.2	194.2	42.39	106.82	283.65	50	1000
			P<0.0001						

The highest value from the two egg counts performed in the pre-treatment assessments was used as the baseline. Analogously, the highest value of the two post-treatment faecal egg counts was used to calculate efficacy. FECR was calculated using arithmetic means.

The significance of FECR in treated and untreated cats was assessed by analysis of variance (ANOVA) following assessment of homogeneity and normality of distribution. The presence of pre- and post-treatment clinical signs of *C. aerophila* infection was considered as a secondary parameter, summarized per group and compared by the Chi-Squared test. Statistical calculations and randomization were performed with the SPSS® statistical package for Windows, version 13.0, nQuery + nTerim 3.0 (StatSols), Statistical Solutions© Ltd. 2014, Microsoft® Excel 2010.

Results

All cats completed the study according to the protocol and were included in the efficacy calculation. None of the cats enrolled in the study showed adverse events during the study. No concomitant treatments were administered to the study animals.

Table 3 Number (n) and percentages of cats showing clinical signs potentially related to *Capillaria aerophila* infection. Number of cats enrolled in G1: 20; number enrolled in G2: 21

Clinical signs	Group	Day 0 n/(%)	Days 7 ± 1 n/(%)	Days 11 ± 1 n/(%)
Dyspnoea	G1	2 (10.0 %)	0	0
	G2	0	0	0
Broncho-vesicular sounds	G1	1 (5.0 %)	1 (5.0 %)	0
	G2	2 (9.5 %)	2 (9.5 %)	2 (9.5 %)
Sneezing	G1	8 (40.0 %)	5 (25.0 %)	2 (10.0 %)
	G2	4 (19.0 %)	4 (19.0 %)	5 (23.8 %)
Wheezing	G1	1 (5.0 %)	0	0
	G2	1 (4.8 %)	1 (4.8 %)	1 (4.8 %)
Cough	G1	3 (15.0 %)	0	0
	G2	1 (4.8 %)	1 (4.8 %)	1 (4.8 %)
Nasal discharge	G1	3 (15.0 %)	2 (10.0 %)	1 (5.0 %)
	G2	5 (23.8 %)	6 (28.6 %)	5 (23.8 %)
Number of cats with at least 1 sign	G1	11 (55.0 %)	7 (35.0 %)	2 (10.0 %)
	G2	7 (33.3 %)	8 (38.1 %)	8 (38.1 %)

Pre-treatment egg counts

At baseline, study cats had an average of 180 (s.d. = 135.1, 95 % CI from 116.75 to 243.25) and 223.8 (s.d. = 202.3, 95 % CI from 131.75 to 315.87) *C. aerophila* EPG in G1 and G2 respectively (Table 2).

Efficacy evaluation

All cats in G1 were negative for *C. aerophila* eggs, while animals in G2 were persistently infected with an average of 195.2 EPG (s.d. = 194.2, 95 % CI from 106.82 to 283.65). Differences in mean EPG values were statistically significant at all time points post-treatment ($p < 0.001$) (Table 2). Treatment with Advocate® spot-on showed an efficacy of 100 % in reducing outputs of *C. aerophila* eggs.

Clinical income and outcome

On day 0, 11 cats in G1 (55 %) and 7 cats in G2 (33.3 %) showed at least one clinical sign potentially related to the infection, i.e. dyspnoea, broncho-vesicular sounds, sneezing, wheezing, cough and nasal discharge (Table 3). On the day the study was completed (days 11 ± 1), 9 cats in G1 had fully recovered, while 2 had persisting clinical signs (Table 3). The two post-treatment symptomatic G1 cats showed an improvement in their health following the treatment: in one case the cat showed dyspnoea and sneezing before treatment and only sneezing after treatment, while in the second case sneezing, wheezing and nasal discharge were present before treatment and only sneezing and nasal discharge persisted clinically. All symptomatic cats belonging to G2 still had symptoms potentially related to the infection at the post-treatment examinations.

Discussion

The present study demonstrated that a single administration of Advocate® at the recommended dose is 100 % efficacious in the treatment of *C. aerophila* infection in cats based on faecal egg output.

Additionally, the combination was safe as no cats suffered any adverse events.

The complete recovery of 9 out of 11 cats with one or more respiratory signs following treatment with Advocate® spot-on, along with the persistency of clinical signs in untreated control animals, supports the evidence for the high efficacy of this parasiticide in the treatment of lung capillariosis of cats. The incomplete disappearance of clinical signs at the post-treatment evaluation of two G1 cats suggests that adult *C. aerophila* living beneath the respiratory system epithelium of the host may cause severe sub-mucosal lesions that may require more than two weeks to restore the full integrity of the mucosa and achieve disappearance of the clinical signs. Remarkably, these two cats showed a 100 % reduction in outputs of *C. aerophila* eggs.

Data obtained in this study confirm previous findings on the efficacy of moxidectin in the treatment of *C. aerophila* in cats. In fact, a recent study showed a 99.79 % reduction of *C. aerophila* egg counts in Advocate®-treated animals in comparison with cats left untreated (Traversa et al. 2012).

In summary, this information is of high interest from a clinical viewpoint considering that no drugs are currently marketed with *C. aerophila* as an indication for use in cats and that, in general, information on the field efficacy of parasiticides in the treatment of pulmonary capillariosis in cats is poor. In fact, various molecules (e.g. dichlorvos, different dosages of injectable or oral levamisole, off-label ivermectin and abamectin) have been evaluated in the past but the vast majority of these data are limited to a few animals or based on *off-label* no-GCPV protocols (Norsworthy 1975; Endres 1976; Blagburn et al. 1987; Barrs et al. 2000; Bowman et al. 2002; Foster et al. 2011).

More recently, the safety and efficacy of a topical combination containing the macrocylic lactone eprinomectin (Broadline®, Merial) was evaluated in two GCPV studies (Rehbein et al. 2014; Knaus et al. 2015). An efficacy of 99.6 % in reducing counts of *Capillaria* eggs was reported after treatment with eprinomectin in naturally infected cats (Rehbein et al. 2014). Although species-specific identification of the eggs was not performed in the above mentioned study, it was considered unlikely that the eggs belonged to a species other than *C. aerophila* (Rehbein et al. 2014). Later, a single treatment with eprinomectin was able to reduce the *C. aerophila* parasite burden (efficacy 82.4 %, $p = 0.016$) and to lower faecal egg shedding (reduction 93.5–99.1 %, $p = 0.01$) in naturally infected cats (Knaus et al. 2015).

Also, a case of co-infection by *C. aerophila* and the respiratory metastrongyloid *Troglostrongylus brevior* was successfully treated with a single dose of a spot-on formulation containing emodepside 2.1 %/praziquantel 8.6 % (Profender®, Bayer Animal Health) (Di Cesare et al. 2015b).

Both eprinomectin and emodepside are effective in treating the worldwide distributed infection by the "cat lungworm" *Aelurostrongylus abstrusus* (Traversa et al. 2009b; Knaus et al. 2014; Bohm et al. 2015). Furthermore, a spot-on parasiticide containing moxidectin 1 % (Advocate; Bayer Animal Health) has been shown to be effective in stopping larval shedding and curing clinical signs in naturally *A. abstrusus*-infected cats (Traversa et al. 2009c) and it is licensed in some markets (e.g. Australia) for the treatment of cat aelurostrongylosis.

In view of the current spread of lungworms either in single or co-infections (Di Cesare et al. 2015a), great clinical importance attaches to the availability of easy-to-apply spot-on formulations containing macrocyclic lactones (e.g. moxidectin, eprinomectin) or cyclooctadepsipeptides (e.g. emodepside) that are simultaneously effective against more than one species of respiratory nematodes.

For instance, further studies on a large scale are warranted to evaluate the potential efficacy of emodepside in treating *T. brevior* and *C. aerophila* infection and, importantly, of moxidectin in the therapy of cat troglostrongylosis. Indeed, the available information suggests that *T. brevior* severely affects kittens and young cats and may be life-threatening (Di Cesare et al. 2014b, 2015b;

Traversa et al. 2014; Crisi et al. 2015). Prompt and effective anthelmintic therapy is thus of importance in treating the infection (Traversa and Di Cesare 2016).

A single application of Advocate® at the recommended dosage leads to a high moxidectin concentration and a long elimination half-life, providing prolonged activity against major feline parasites. Moreover, it has been shown that monthly administration of the formulation results in a steady-state of moxidectin in the blood that is able to reduce and/or prevent hookworm and infections in experimentally infected animals with *Dirofilaria immitis* (Cruthers et al. 2008; Little et al. 2015). At this elevated plasma level, moxidectin has the potential to prevent the development of lungworm larvae; further studies are important to evaluate the efficacy of moxidectin 1% in preventing *C. aerophila* and, more generally, lungworm infections.

In conclusion, the safety and efficacy of Advocate® make it a suitable choice for the treatment of cat lung capillariosis. The advantage of this easy-to-apply spot-on formulation lies in its broad spectrum of activity against a wide range of feline nematodes but also in the ease of application in indocile or feral animals.

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Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed were in accordance with the ethical standards of the institution or practice at which the study was conducted. This article does not contain any studies with human participants performed by any of the authors.

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Conflict of interest

The authors Angela Di Cesare, Fabrizia Veronesi, Gioia Capelli, Fabrizio Solari Basano, Roberto Nazzari, Barbara Paoletti and Donato Traversa declare that they have no conflict of interest. The authors Katrin Deuster and Roland Schaper are employees of Bayer Animal Health GmbH which sponsored the present study.

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