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▶ **To cite this version:**

Mélanie Legain, A. Idee, D. Mardini, Magalie René-Martellet, Marion Mosca. Efficacy and innocuity of lotilaner in the treatment of otodectic mange in ferrets. Veterinary Parasitology, 2024, 332, pp.110317. 10.1016/j.vetpar.2024.110317 . hal-04767419

HAL Id: hal-04767419
https://hal.inrae.fr/hal-04767419v1

Submitted on 5 Nov 2024

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Veterinary Parasitology 332 (2024) 110317

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Efficacy and innocuity of lotilaner in the treatment of otodectic mange in ferrets

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ARTICLE INFO

Keywords:
Otodectes cynotis
Ear mites
Isoxazoline
Otology
Ectoparasite

ABSTRACT

Otodectes cynotis is a contagious ear mite generally responsible of a parasitic otitis. This prospective study evaluates the efficacy, safety and impact on quality of life (QoL) of oral lotilaner for the treatment of *Otodectes* infestation in ferrets. Ferrets of weight greater than 500 g, with *Otodectes* mites confirmed on ear swabs examination and that did not receive an acaricidal treatment in the previous two weeks were included. Oral lotilaner (Credelio 12 mg, ELANCO FRANCE, Sèvres, France) was administered at inclusion day (D0) and 28 days later (D28). Parasitic counts and clinical examination were performed at D0, D28 and D56. A QoL and owner satisfaction questionnaire was given at D0 and D56. Statistical analysis was performed with Shapiro-Wilk test for normality and Wilcoxon test for mean comparison (significance: $p<0.05$). Eleven ferrets were included, two were asymptomatic. Mean weight was 1.2 kg (0.68–2.66). Mean lotilaner dose was 12.3 mg/kg (9–17.6). Mean eggs, adults or nymphs, larvae, and fragments counts were 30.4 (3–104), 11.2 (1–61), 5.4 (0–36), 3.5 (1–7) respectively at D0; 0, 0, 0.1 (0–1), 0.5 (0–3) respectively at D28; 0, 0, 0, 0.14 (0–1) respectively at D56. Differences were statistically significant from baseline in all cases ($p<0.05$). Pruritus was absent in all cases at D56. No adverse effects were reported. All owners were "completely satisfied" with the treatment. Mean impact of the disease on QoL was 4.5/18 (SD=4.15) at D0 and 0 at D56 (significant difference, $p<0.05$). Oral lotilaner appears as a safe, efficient, easy to use and satisfactory treatment of *Otodectes cynotis* infestation in ferrets.

1. Introduction

Ferrets are popular pets. There are about 100,000 in the UK and 501,000 in the USA (Dancer et al., 2022a). They are also used as working animals for pest control and as laboratory animals for research (model species in SARS-CoV-2 research) (Dancer et al., 2022b). Otodectic mange is a frequent disease of ferret's ear canals caused by *Otodectes cynotis*. According to a Japanese study, otodectic mange is the fourth most common disease of ferrets after adrenal diseases, insulinomas and diarrhea with an incidence of 6.1 % (16 ferrets among 246) (Miwa et al., 2009). This mite is considered as the most frequent in companion animals (Franc, 2005) and affects dogs, cats, foxes, ferrets, Patagonian cavies and others wild animals (Briceño et al., 2020; Cruz et al., 2017; Heyning and Thienpont, 1977; Huang-Bastos et al., 2020; Patterson and Kirchain, 1999; Taenzler et al., 2017; Tyler et al., 2020). The disease is contagious, very rarely zoonotic (Heyning and Thienpont, 1977) and transmitted by contact with infected animals (Halck et al., 2023). The life cycle of *Otodectes cynotis* is entirely completed within the ear of the animal in about three weeks and is composed of four stages: egg, larvae, nymph and adult (Otranto et al., 2004). The female mite lays around twenty eggs during its lifetime of a few weeks (Saari et al., 2019). Ferrets can be asymptomatic or present head shaking, pruritus, mild to abundant brown cerumen, excoriations, and aural hematomas secondary to scratching (Le Sueur et al., 2011). Diagnosis is made by ear swabbing and microscopic observation of the parasite. Bacterial or yeast complications are frequent. Treatment usually relies on topical ectoparasiticides such as selamectin (Halck et al., 2023) or imidacloprid 10 %/moxidectin 1.0 % (Le Sueur et al., 2011) but the efficacy and ease-of-use of these treatments are sometimes unsatisfying (Patterson and Kirchain, 1999). Lotilaner is a recent molecule belonging to the family of isoxazolines. These molecules are marketed for dogs and cats and have a wide security margin and high efficacy on numerous mites

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https://doi.org/10.1016/j.vetpar.2024.110317
Received 12 July 2024; Received in revised form 16 September 2024; Accepted 16 September 2024
Available online 17 September 2024
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including *Otodectes cynotis* (Zhou et al., 2022a). Isoxazolines have been used in numerous species including dogs, cats, rabbits, golden hamster, zoo birds, bears or monkeys (Azaria and Defalque, 2023; Wick et al., 2020; Yarto Jaramillo et al., 2020). Although adverse events have been rarely reported with the labeled formulations (vomiting, diarrhea, ptyalism, tremors, seizures), none of the studies performed in extra-label hosts have reported adverse events. The aim of this study is to evaluate the efficacy and innocuity of monthly lotilaner administration for the treatment of naturally acquired *Otodectes cynotis* infestation in ferrets under field conditions.

Table 1
Detailed results of quality-of-life survey before and after the lotilaner treatment. NC = Not concerned because the owner 3 does not answer the survey.

Before treatment	Answer	Owner 1	Owner 2	Owner 3	Owner 4	Owner 5	Owner 6	Owner 7	Owner 8	Owner 9	Owner 10	Owner 11
Were you concerned about the severity of your ferret's illness	0 = not concerned; 3 = very concerned	1	1	NC	1	2	0	0	0	2	2	2
Has your ferret's illness had an impact on its behavior and/or mood (slower, more nervous, more aggressive, …)?	0 = no impact; 3 = high impact	2	2	NC	0	1	0	0	0	3	3	3
Was your ferret's sleep disturbed by the illness?	0 = no impact; 3 = high impact	3	3	NC	1	1	0	0	0	3	3	3
Are your ferret's meals affected by the disease (reduced appetite, itching during meals, …)?	0 = no impact; 3 = high impact	1	1	NC	0	0	0	0	0	1	1	1
Were your ferret's activities and games disrupted by the disease (more tired, nervous, itchy, …)?	0 = no impact; 3 = high impact	1	1	NC	1	1	0	0	0	2	2	2
Did your ferret's illness affect its relationship with you, other family members or other animals? (Because of mood changes, skin lesions, …)?	0 = no impact; 3 = high impact	1	1	NC	0	1	0	0	0	0	0	0
Does your ferret's illness change his habits (changes in where he's allowed to sleep, where he eats, how he walks, …)?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Has your ferret been affected by treatment?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Did you find administering the tablets easy?	0 = very difficult; 3 = very easy	1	1	NC	3	2	2	2	3	3	1	3
After treatment												
Are you satisfied with your ferret's current condition (ears, itching, earwax)?	0 = very satisfied; 3 = not satisfied	0	0	NC	1	0	0	0	0	0	0	0
Has your ferret's illness now had an impact on its behavior and/or mood (slower, more nervous, more aggressive, …)?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Is your ferret's sleep now disturbed by illness?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Are your ferret's meals now affected by the disease (no appetite, itching during meals, …)?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Are your ferret's activities and games now disrupted by the disease? (More tired, nervous, itchy, …)?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Has your ferret's illness affected its relationship with you, other family members or other animals? (Because of mood changes, skin lesions, …)?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Does your ferret's illness change his habits? (Changes in where he's allowed to sleep, where he eats, how he walks, …) ?	0 = no impact; 3 = high impact	0	0	NC	0	0	0	0	0	0	0	0
Are you satisfied with the lotilaner treatment for your ferret's ear mange?	0 = not satisfied; 3 = very satisfied	3	3	NC	3	3	3	3	3	3	3	3

2. Materials and methods

2.1. Ethics

This trial was done under good general condition and in accordance with local legislation on the use of patients for clinical trials. All procedures were approved beforehand by our university's Institutional Animal Care and Use Committee with register number 2246. Informed consent was obtained from all ferret owners prior to enrollment of the animals

2.2. Study design

Included animals corresponded to ferrets without gender or age criteria with ear mites (in at least one ear). Reasons for exclusion were weight less than 500 g or acaricide treatment within the last two weeks prior to D0. The study protocol was composed by three visits. "D0" was the inclusion visit (data collection, clinical dermatological and otoscopic examinations, cytological and direct cerumen examination, parasitic count and first treatment, quality-of-life survey). "D28" was the first follow-up visit, 28 +/- 2 days after inclusion, where clinical dermatological and otoscopic examinations, cytological and direct cerumen examination, parasitic count, owner compliance assessment, and second treatment were performed. "D56" was the study termination, 56 +/- 4 days after inclusion, where clinical dermatological and otoscopic examinations, cytological and direct cerumen examination, parasitic count, owner compliance and quality-of-life survey were performed.

2.3. Treatment protocol

Each ferret received at D0 and D28 one tablet of lotilaner (Credelio® 12 mg). One ferret received two tablets because it weighed more than 1 kg. Tablets were always given with a meal. Ears were not cleaned during the study period.

2.4. Clinical evaluation and assessment of O. cynotis infestation

Clinical, dermatological examinations and parasitic counts were performed at each visit. Ears were examined with a handheld otoscope before ear sampling in order to identify the visual presence of mite movement in the ear canal. Direct examination of cerumen was performed by rolling the ear swab in both external ears canal, then spreading cerumen on a glass slide in lactophenol. The microscopic examination was performed using a magnification of 40x or 100x. All parasite stages were counted: eggs, larvae, adults or nymphs and fragments, defined as parts of a mite where stage could not be determined.

2.5. Quality-of-life survey

A quality-of-life survey, inspired by a quality-of-life survey of cats with skin disease (Noli et al., 2016) (Table 1) was completed by owners at D0 and D56. Seven questions regarding quality-of-life of the ferret before and after the treatment (severity of the disease, impact on behavior, sleep, dietary behavior, activities and games, relationships with owner and habits). Two questions were about the ease of use of the treatment. A score from 0 (no impact, easy-to-use treatment) to 3 (high impact, difficult-to-use treatment) was given by the owner for each question. The maximum score was 21 for the quality of life, 6 for the ease of use of treatment. One question, scored from 0 to 3, regarding the owner satisfaction with treatment (3 corresponding to an excellent satisfaction) was added.

2.6. Statistics

Statistical analysis was performed using GraphPad Prism 9.0. Data normality was analyzed using the Shapiro-Wilk test. The Wilcoxon test was performed to compare mean parasitic count between D0 and D56. The signification level was set at $p \leq 0.05$. With a minimal power of 80 % and a significance level of 5 % to have a mean difference in parasitic count of 20, the appropriate number of study animals was calculated at 6.

3. Results

Eleven privately-owned ferrets with ear mites in at least one ear were recruited by Veterinary University Hospital Center of Lyon (VetAgro Sup, France), over a period of 11 months (from February 2022 to January 2023). They were between 7 months and 4 and a half years old (mean age was 21 months) and weighed between 0.7 and 2.6 kg (mean weight was 1.2 kg) (Supplemental Material 2). There were seven female and four male ferrets. The mean lotilaner dose was 12.3 mg/kg (9–17.6 mg/kg). Only ten ferrets completed the study as ferret n°3 was lost to follow-up. At D0, most ferrets (9/11–82 %) showed pruritus. The mean parasitic count at D0 was 5.4 (0–36) adults or nymphs, 11.2 (11–61) larvae, 30.4 (3–104) eggs and 3.5 (1–7) fragments (Fig. 1). At D28, 3/10 ferrets (30 %) had pruritus and the number of parasites was reduced by 100 % for eggs and larvae, by 98 % for adults or nymphs and 81 % for fragments. The mean number of each parasitic stage was significatively lower ($p < 0.05$). At D56, no ferret showed pruritus and the number of parasites was reduced by 100 % for eggs, larvae and adults or nymphs and by 97.4 % for fragments (Supplemental Material 1). The mean number of each parasitic stage was still significatively lower ($p < 0.05$) than baseline.

Based on clinical examination and questioning owners, no adverse effects related to the product were described during the whole time of the study.

The mean score of the quality-of-life survey at D0 and D56 was 6/21 [3–11] and 0.1/21 [0,1] respectively. Seventy percent of owners (n=7) found the treatment easy to use and 100 % (n=10) were totally satisfied by the treatment with lotilaner (Table 1).

4. Discussion

The administration of oral 9–17.6 mg/kg lotilaner dose was effective in curing 60 % of ferrets (6/10) at D28 after one treatment and 100 % at D56 after two treatments. The reported efficacy was similar for a combination of imidacloprid 10 % and moxidectin 1.0 % spot on (Advocate® spot on for small cats and ferrets). Seventy-seven percent (30/39 ferrets) were cured after 1 month (2 treatments at D0 and D14) and 100 % were cured after 56 days and three treatments (Le Sueur et al., 2011). Other treatments have been used for otodectic mange in ferrets. Subcutaneous ivermectin (0.4 mg/kg every 14 days) seems to be ineffective to treat ear mange as only 3/11 ferrets were free of mites after 8 weeks of treatment (Patterson and Kirchain, 1999). Topical treatment with thiabendazole (two drops in each canal once daily for 7 days, every other week) or ivermectin (0.4 mg/kg, diluted 1:10 in propylene glycol every 14 days) showed similar efficacy to lotilaner with 4/5 and 10/10 ferrets free of ear mites after 8 weeks respectively (Patterson and Kirchain, 1999). Single administration of selamectin (45 mg, a complete 0.75 mL single-dose tube) administered topically between the shoulder blades, without cleaning the external ear canal, may be effective but the study did not report a precise percentage of recovery and multiple administrations were sometimes needed (Miller et al., 2006). Anecdotal reports described the use of topical fipronil (0.1–0.15 mL in each ear canal every 14 days for two to three treatments) (Miller et al., 2013) but the size of the ear canal in ferrets makes intra-auricular treatments difficult. Among all these treatments, lotilaner was the first oral option described for otacariosis in ferrets.

Isoxazoline use has never been described in ferrets but their mode of action ensure a high margin of safety for use in veterinary species as isoxazolines only block invertebrate glutamate-gated chloride channels and GABA-gated chloride channels (Gassel et al., 2014). Thus,

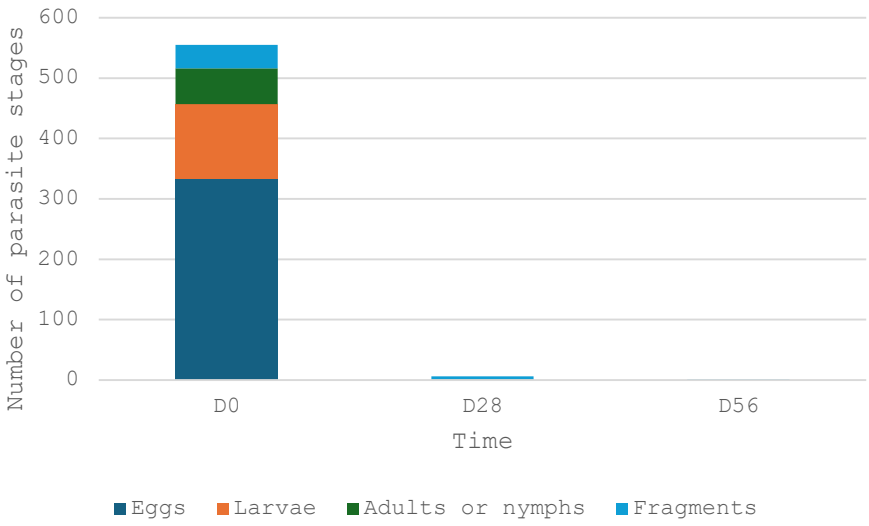

Fig. 1. Number of Otodectes Cynotis stages (eggs, larvae, adults or nymphs and fragments of parasite) among time. D0 is the inclusion time. D28 is one month after the first administration of lotilaner tablet. D56 is one month after the second administration of lotilaner tablet.

isoxazolines have been off-label used safely in many species. A golden hamster with demodicosis was treated with a single oral dose of fluralaner without adverse effects (Azaria and Defalque, 2023). Thirty rabbits with sarcoptic mange and 15 with psoroptic mange were treated by a single oral dose of fluralaner without adverse effects. Nineteen rabbits with psoroptic mange were treated with a single dose of an oral combination of afoxolaner-milbemycin without adverse effect (Azaria and Defalque, 2023). The choice of lotilaner among all isoxazolines for treating ear mites in ferrets was based on a pre-existing on-label use for cats and the galenic (oral tablet). In this study, no adverse effects were observed in ferrets treated with two doses of lotilaner suggesting a good innocuity. The efficacy of isoxazolines in ferrets was not known but the efficacy of isoxazolines in otodectic mange in other species is well-documented. Efficacy of isoxazolines was evaluated in 213 dogs enrolled in 5 studies, and in 245 cats enrolled in 7 studies (Azaria and Defalque, 2023). Oral afoxolaner yielded a reduction in ear mites of more than 99.5 %, 28 days after treatment (Azaria and Defalque, 2023; Carithers et al., 2016; Machado et al., 2018; Panarese et al., 2021). Topical afoxolaner was used in 79 cats with 99.9 % in reduction in ear mites at day 32 (Azaria and Defalque, 2023). Cats treated with oral or topical fluralaner or sarolaner were all mite free one month after treatment (Azaria and Defalque, 2023; Bosco et al., 2019; Ribeiro Campos et al., 2021; Six et al., 2016; Taenzler et al., 2018, 2017). In dogs, a reduction in mites of 99.8 % or 98.2 % at day 28 was observed with fluralaner or sarolaner, respectively (Azaria and Defalque, 2023; Ribeiro Campos et al., 2021; Six et al., 2016). Lotilaner has not been tested for the treatment of otodectic mange in animals but pharmacodynamics of isoxazolines used was similar (Zhou et al., 2022b). In our study, two oral doses of lotilaner at 28 days interval were effective in curing 100 % of ferrets at D56. The life cycle of *Otodectes cynotis* usually takes 3 weeks (Saari et al., 2019) and lotilaner persists in canine and feline blood for about 30 days (Toutain et al., 2018, 2017). After one tablet of lotilaner, no larvae or eggs were observed at D28. Thus, a single dose of lotilaner may be sufficient to eradicate ear mites at D56. In this study, 82 % of ferrets had pruritus at D0 whereas previous studies report that ferrets are mostly asymptomatic (Halck et al., 2023; Le Sueur et al., 2011). This could be explained by a recruitment bias since the reason for consultation was often pruritus. Ferrets who did not show pruritus were often housemates of the initial patient.

Direct examination of cerumen was performed by rolling the ear swab in both external ear canals, then spreading cerumen on a glass slide in lactophenol. Other sampling methods were described in cats, by flushing the ear canals with 1 or 2 mL of mineral oil or aqueous solution (Docusol 5 %®) with a glass dropper (Becskei et al., 2017; Tyler et al., 2020) or by using a Volkmann's curette to sample cerumen (Combarros et al., 2019). Ears were then vigorously massaged, and the material aspirated using the same dropper. This method was not chosen because of the small size of ferret ears and the difficulty of ferret restraint.

Most of owners found the treatment easy to use and all were "totally satisfied" with it. According to the authors knowledge, this is the first study on otodectic mange to include a quality-of-life survey.

The satisfaction of owners and the efficacy of treatment make lotilaner a new treatment option and the first oral treatment option for otodectic mange in ferrets.

The study presents some limitations. First, different operators had collected cerumen and operator experience may have changed results but the protocol was detailed, clear and easy to reproduce. There was no objective clinical score (pruritus, cerumen) for otodectic mange in ferrets, and the OTIS score (Otitis Index Score) should have been done to evaluate clinical improvement more precisely. A randomized double blinded prospective non-inferiority study would be preferable to compare treatments but would necessitate a larger number of cases.

5. Conclusion

Oral lotilaner treatment (9–17.6 mg/kg) achieved a 100 % reduction in adults or nymphs, larvae and eggs of *Otodectes cynotis* in ferrets after 2 administrations at one-month intervals. No adverse effects have been reported based on clinical examination, and all the owners were satisfied by the treatment. This is the first study showing oral lotilaner efficacy and safety in the treatment of otodectic mange in ferrets and lotilaner safety in ferrets and the first description of an oral treatment option for otodectic mange in ferrets.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.vetpar.2024.110317.

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