



Original Article

Topical treatment of external otitis in cats with combination of levofloxacin, miconazole and dexamethasone

Tratamento tópico de otite externa em gatos com a associação de levofloxacina, miconazol e dexametasona

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ABSTRACT

The objective of this work was to evaluate the efficacy of a topical formulation containing levofloxacin, miconazole, and dexamethasone in the treatment of external otitis in cats. Eighteen cats showing clinical signs of external otitis—in the video otoscopy examination and cerumen cytology—were evaluated. The animals were divided into three groups of six animals. Group 1 (G1) was the control group; Group 2 (G2) was treated with a combination of 0.5% levofloxacin, 2% miconazole, and 0.02% dexamethasone, using distilled water as the vehicle; and Group 3 (G3) was treated with the same combination, using vegetable glycerin as the vehicle. The animals were reassessed weekly; animals in G1 had no improvement of clinical signs of otitis or in the findings in the cerumen cytology. However, animals in G2 and G3 showed improvement of clinical signs, and control of yeasts and/or bacteria in the cytological examination of the ear after seven days of treatment. Based on the results, the formulation containing the combination of levofloxacin, miconazole, and dexamethasone was effective in controlling the perpetuating factors of external otitis in cats.

RESUMO

O objetivo deste trabalho foi avaliar a eficácia de uma formulação tópica contendo levofloxacina, miconazol e dexametasona no tratamento da otite externa em gatos. Foram utilizados 18 gatos que apresentavam sinais clínicos de otite externa no exame de videotoscopia e na citologia do cerúmen. Os animais foram divididos em três grupos com seis animais cada. O grupo 1 foi o grupo controle; grupo 2 foi tratado com a associação de levofloxacina 0,5%, miconazol a 2% e dexametasona 0,02% sendo o veículo água destilada; já o grupo 3 foi medicado com a mesma associação, sendo o veículo glicerina vegetal. Os animais foram reavaliados semanalmente e os animais do grupo controle não tiveram melhora dos sinais clínicos de otite e nos achados na citologia de cerúmen. No entanto, os animais do grupo 2 e 3 apresentaram melhora dos sinais clínicos e no controle de leveduras e/ou bactérias no exame citológico de ouvido a partir de sete dias de tratamento. Com base nos resultados foi possível concluir que a formulação contendo a associação levofloxacina + miconazol + dexametasona foi eficaz no controle dos fatores perpetuantes da otite externa em gatos.

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INTRODUCTION

Otitis is a term related to ear inflammation, which can be classified, according to its anatomical location, as: external, medium, or internal (MORIELLO; DIESEL, 2006).

Occurrence of otitis in cats is little reported due to the lack of clinical signs, however, Hill et al. (2006) reported that it is the third most common dermatological problem found in feline clinical routine, preceded by flea infestation and abscesses.

The pathogenesis for the development of external otitis involves the interaction of predisposing factors, primary causes, and perpetuating factors. Different from the dogs, the conformation of the auditory conduit in cats is not an anatomical problem for the development of otitis; however, humid environments and excessive cleaning, performed by humans or other cats, can be predisposing factors (AUGUST 1988; KOCH 2016).

The primary causes of otitis are directly related to atrial disease and comprise parasitic causes (*Otodectes cynotis*, *Demodex cati*), allergies, autoimmune diseases, polyp, or foreign bodies. The perpetuating factors are those that prolong the inflammatory process and delay healing, including the presence of opportunistic infections caused by bacteria or fungi (KONTOS; SOTIRAKI; HIMONAS et al., 1998; GUAGUÉRE; MULLER; DEGORCE et al., 2001; SOTIRAKI et al., 2001).

The clinical signs may be unilateral or bilateral, such as erythema, alopecia and ulcerated lesions near the auricle, pruritus, pain, and change in ear shape, in addition to behavioral changes (aggressiveness or hyporexia) (PEREGO et al., 2014).

The treatment of external otitis consists in removing the primary cause, reducing inflammation, and controlling perpetuating factors. Topical treatment is indicated as initial therapy, although it is often not well accepted by cats and their owners (MORIELLO; DIESEL, 2006).

Most otological products available in the pet market for treatment of otitis have antibiotic, antifungal, and anti-inflammatory associations due to the mixed nature of secondary infection by bacteria and fungi. The antibiotics most frequently found in these products are from the aminoglycoside class, which are highly ototoxic and may lead to deafness. Fluoroquinolones, such as levofloxacin and ciprofloxacin, have a broad spectrum of action and do not cause ototoxicity as a side effect (MORIELO; DIESEL, 2006; KENNIS, 2013).

Therefore, the objective of this study was to evaluate the efficacy of a topical formulation containing levofloxacin (0.5%), miconazole (2%), and dexamethasone (0.02%) in the treatment of perpetuating factors of external otitis in cats.

MATERIAL AND METHODS

This study was approved by the Committee for Ethics in Animal Use of the Veterinary Institute of the Federal Rural University of Rio de Janeiro (CEUA-IV-UFRRJ; protocol number 8038280317).

Eighteen adult mixed-breed cats, without distinction of sex, were evaluated. These animals had no contact with any type of medication for a period of 60 days and presented clinical signs of otitis, which were confirmed by cytology showing presence of the perpetuating agents (bacteria or yeasts). Cats that presented mites, polyps, or neoplasia were not used for the otoscopy.

The cats were divided into three groups with six animals by similarity in otological evaluation scores for the pre-treatment evaluation. Group 1 (G1) (control) was treated with placebos (containing distilled water and vegetable glycerin) at 0.5 ml, instilled into the ear canal. The animals in Group 2 (G2) were treated with 0.5 ml of a formulation containing 0.5% levofloxacin, 2% miconazole, and 0.02% dexamethasone, using distilled water as the vehicle. The animals in Group 3 (G3) were treated with the same dose and formulation used in the G2, but using vegetable glycerin as the vehicle. All animals were medicated every 24 hours for 15 consecutive days.

The animals were evaluated for presence of clinical signs of external otitis at days -2, +7, +14 +21, and +28, through video otoscopy using a UB CAM Pro™. The clinical signs of exudate, erythema, hyperpigmentation, and hyperkeratosis were evaluated according to the classification used by Rougier et al. (2005) and Engel et al. (2010): 0 = normal, 1 = mild, 2 = moderate, and 3 = severe. The clinical signs of odor, pruritus, and pinnal-pedal reflex were classified by their presence or absence, attributing scores 1 and 0, respectively. After the evaluation of the animal, a score was given for each criterion; a total ≥ 5 was considered compatible with otitis.

Cytological examination of the auditory canal was performed at days -2, +7, +14 +21, and +28. The classification used to determine the scores considered the bacterial / yeast morphological units per field as follows: absent (-) when presenting up to five; small amounts (+) when presenting 6 to 10; mean infection (++) when presenting 10 to 20; and high infection (+++) when presenting above 21. The observations were performed using 400x magnification.

Statistical analysis was carried out considering one ear as one experimental unit, the reduction of the scores of clinical signs, and cytological examination. The BioEstat 5.3 program was used, considering a level of significance of 5%. The Shapiro-Wilks test was performed to determine the normality of the data. The means of the reduction of scores was compared using ANOVA followed by the Tukey's test.

RESULTS

All animals had bacterial and/or yeast scores higher than two at day -2. The scores of the animals in G1 (control)

remained high throughout the study. The yeast found as a perpetuating factor in the animals was *Malassezia* spp.; the results of the reduction of scores for yeast are shown in Table 1.

Table 1 – Results of the scores found by otological cytology for *Malassezia* sp. in cats in three experimental groups at days +7, +14, +21, and +28.

	D -2			D +7			D +14			D +21			D+28		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
0	2	2	2	2	7	7	0	8	8	2	10	8	0	10	8
1	1	0	0	0	5	4	2	4	4	0	1	3	2	2	4
2	4	6	6	3	0	1	5	0	0	5	1	1	4	0	0
3	5	4	4	7	0	0	5	0	0	5	0	0	6	0	0
TE	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
M	2.0 ^a	2.0 ^a	2.0 ^a	1.2 ^a	0.4 ^b	0.5 ^b	2.2 ^a	0.3 ^b	0.3 ^b	2.1 ^a	0.2 ^b	0.4 ^b	2.3 ^a	0.1 ^b	0.3 ^b
DP	1.1	1.0	1.0	1.1	0.5	0.6	0.7	0.5	0.5	1.1	0.6	0.6	0.7	0.3	0.4
p	0.99			<0.01			<0.01			<0.01			<0.01		

0 (normal); 1 (mild); 2 (moderate); 3 (severe); TE = total ears; M = mean; SD = standard deviation; p = p-value. Note: ANOVA test followed by the Tukey's test. Letters other than b indicate a statistically significant difference.

Table 2 – Results of the scores found by otological cytology for bacteria in cats in three experimental groups at days +7, +14, +21, and +28.

	D -2			D +7			D +14			D +21			D+28		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
0	6	8	8	5	12	12	4	4	8	6	6	10	6	6	10
1	3	2	2	2	0	0	3	5	2	0	5	2	0	6	2
2	1	0	0	3	0	0	3	3	2	6	1	0	3	0	0
3	2	2	2	2	0	0	2	0	0	0	0	0	3	0	0
TE	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
M	0.9 ^a	0.6 ^a	0.6 ^a	1.1 ^a	0 ^b	0 ^b	1.2 ^a	0.9 ^b	0.5 ^b	1 ^a	0.5 ^b	0.1 ^b	1.2 ^a	0.5 ^b	0.1 ^b
DP	1.1	1.1	1.1	1.2	0	0	1.1	0.7	0.7	1.0	0.6	0.3	1.3	0.5	0.1
p	0.83			<0.01			<0.01			<0.01			0.01		

0 (normal); 1 (mild); 2 (moderate); 3 (severe); TE = total ears; M = mean; SD = standard deviation; p = p-value. ANOVA test followed by the Tukey's test. Letters other than b indicate a statistically significant difference.

Table 3 – Results of scores in the clinical evaluation of exudate in cats in three experimental groups at days +7, +14, +21, and +28.

	D -2			D +7			D +14			D +21			D+28		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
0	0	0	0	0	0	0	0	0	3	0	1	2	1	3	6
1	0	0	0	0	8	6	1	7	3	2	6	7	2	5	2
2	4	5	3	4	4	6	3	1	6	4	3	2	3	4	4
3	8	7	9	8	0	0	8	4	0	6	2	0	6	0	0
TE	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
M	2.5 ^a	2.6 ^a	2.7 ^a	2.6 ^a	1.3 ^b	1.5 ^b	2.6 ^a	1.7	1.2 ^b	2.3 ^a	1.5	0.9 ^b	2.1	1.1 ^b	0.8 ^b
DP	0.5	0.5	0.4	0.4	0.4	0.5	0.6	0.9	0.9	0.7	0.9	0.8	1.0	0.6	0.8
p	0.71			<0.01			<0.01			0.05			<0.01		

0 (normal); 1 (mild); 2 (moderate); 3 (severe); TE = total ears; M = mean; SD = standard deviation; p = p-value. ANOVA test followed by the Tukey's test. Letters other than b indicate a statistically significant difference.

Table 4 – Results of scores in the clinical evaluation of erythema in cats in three experimental groups at days +7, +14, +21, and +28.

	D -2			D +7			D +14			D +21			D+28		
	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3	G1	G2	G3
0	0	0	0	0	6	0	0	4	6	0	0	4	2	2	5
1	3	0	4	0	2	10	3	4	3	3	7	4	2	6	7
2	5	10	6	6	4	1	6	1	1	7	4	4	8	2	0
3	4	2	2	6	0	1	3	3	2	2	1	0	0	2	0
TE	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
M	2.0 ^a	2.1 ^a	1.8 ^a	2.5 ^a	0.8 ^b	1.2 ^b	2.0 ^a	1.2	0.9 ^b	1.9 ^a	1.5	1.0 ^b	1.5 ^a	1.3	0.58 ^b
DP	0.7	0.3	0.7	0.5	0.9	0.6	0.7	1.2	1.1	0.6	0.6	0.8	0.8	1.0	0.5
p	0.55			<0.01			<0.05			<0.05			<0.05		

0 (normal); 1 (mild); 2 (moderate); 3 (severe); TE = total ears; M = mean; SD = standard deviation; p = p-value. ANOVA test followed by the Tukey's test. Letters other than b indicate a statistically significant difference.

Regarding the bacteria found, cocci bacteria predominate, however, a small quantity of rods were found. The results of the reduction of scores for bacteria when using the tested formulation are shown in Table 2.

Exudate and erythema were the only clinical signs present in the cats evaluated in the present study. No animals with pain, hyperkeratosis, hyperpigmentation, or pinnal-pedal reflex were found. The results of the reduction of scores for exudate and erythema clinical signs are shown in Tables 3 and 4, respectively.

DISCUSSION

Malassezia spp. are the most commonly found yeasts in the auditory canal of cats. Its relation with pathologies depends on associations with clinical signs and not with the quantity observed in cytological examinations (ANGUS, 2004; MORIELLO; DIESEL, 2006). In the present work, all the cats that had *Malassezia* spp. in their auditory canals presented clinical external otitis, therefore, the treatment was justified for these animals.

The scores of cats in G2 and G3 showed statistically significant reductions ($p < 0.05$) from the seventh day of treatment. Scores remained low until the end of the treatment (fourteenth day) and remained low for 14 days after the end of the treatment. There was no statistical difference ($p > 0.05$) when comparing the formulations used in G2 and G3, denoting that the vehicle used does not affect the formulation effectiveness to control fungal infections.

Although cocci and rods were found in the cytological examination of the animals, the identification of the microorganism and their sensitivity to the antibiotic tested was not possible through bacterial culture. However, a statistically significant reduction ($p < 0.05$) was observed in G2 and G3 when compared to the control, showing that they were effective to control the bacterial infection. G2 and G3 presented no statistical difference ($p > 0.05$) in the reduction of scores.

Despite the growing reports on bacterial resistance to antibiotics, the bacteria found in the cats evaluated in the present work were sensitive to levofloxacin; however, other studies should confirm their susceptibility (HARIHARAN et al., 2006; KENNIS, 2013).

The exudate scores reduced after seven days of treatment and remained low up to the twenty-eighth day of evaluation. The formulation used in G3 reduced the exudate earlier than that used in G2. The glycerin in the formulation used in G3 allowed for greater solubilization and facilitated clearance of the cerumen by the animals. This is explained by the lower hydrophilicity of the vehicle in this formulation, which better emulsified the cerumen and reached the site of action more quickly.

The low exudate score found even after the end of the treatment can be explained by the removal of the perpetuating factors—fungal and bacterial infections.

Excess cerumen is produced in response to the chronic inflammation caused by these agents (TATER et al., 2003).

According to the evolution of erythema at the seventh day of treatment, the animals in G2 and G3 presented lower score, with a significant difference when compared to those in G1. However, although the scores of animals in G2 remained low and the cats presented clinical improvement, only those in G3 maintained this statistical difference at days +14, +21, and +28.

The formulations tested in the present study showed excellent results for the control of perpetuating factors of external otitis in cats. This denotes the importance of developing otological products of low ototoxicity, considering the safety of these animals. The treatment prescription should only be suggested to cats that show clinical signs of external otitis.

CONCLUSION

The formulation containing 0.5% levofloxacin, 2% miconazole, and 0.02% dexamethasone, using distilled water or glycerin as the vehicle, is effective for the control of perpetuating factors of otitis in cats.

REFERENCES

- ANGUS, J.C. Otic cytology in health and disease. **Veterinary Clinics of North America: Small Animal Practice**. v.34, n. 2, p.411-424, 2004.
- AUGUST, J.R. Otitis externa: a disease of multifactorial etiology. **Veterinary Clinics of North America: Small Animal Practice**. v.18, n. 4, p.731-742, 1988.
- ENGEL, M.; DE BOCK, M.; HARE, J. et al. Effectiveness of an Otic Product Containing Miconazole, Polymyxin B and Prednisolone in the Treatment of Canine Otitis Externa: Multi-site Field trial in the US and Canada. **International Journal of Applied Research in Veterinary Medicine**. v.8, n. 1, p.21- 30, 2010.
- GUAGUÉRE, E.; MULLER, A.; DEGORCE RUBIALES F. Feline demodicosis: a retrospective study of 12 cases. **Veterinary Dermatology**. v.15, n. 1, p.34-34, 2004.
- HARIHARAN, H.; COLES, M.; POOLE, D. et al. Update on antimicrobial susceptibilities of bacterial isolates from canine and feline otitis externa. **Canadian Veterinary Journal**. v.47, n. 3, p.253, 2006.
- HILL, P.; LO, A.; EDEN, C.A.N. et al. Survey of the prevalence, diagnosis and treatment of dermatological conditions in small animals in general practice. **The Veterinary Record**, v. 158, n. 16, p.158-533, 2006.
- KENNIS, R.A. Feline otitis: diagnosis and treatment. *Vet. Clin. North. Am. Small. Anim. Pract.*, v.43, p.51-56, 2013.
- KOCH, S.N. Feline otitis: diagnosis and treatment. In: 8TH WORLD CONGRESS OF VETERINARY DERMATOLOGY, 230p., 2016, Bordeaux.
- KONTOS, V.; SOTIRAKI, S.; HIMONAS, C. Two rare disorders in the cat: demodectic otitis externa and sarcoptic mange. **FelinePractice**, v.1, n.1, p.23-29, 1998.
- MORIELLO, K.A.; DIESEL, A. Manejo Médico da Otite. In: AUGUST, J.R. (6 Ed) **Medicina Interna de Felinos**. Rio de Janeiro: ELSEVIER, 2006. p. 348 - 358.

PEREGO, R.; PROVERBIO, D.; BAGNAGATTI DE GIORGI, G. et al. Prevalence of otitis externa in stray cats in northern Italy. **Journal of Feline Medicine and Surgery**. v.16, n. 6, p.483-490, 2014.

ROUGIER, S.; BORELL, D.; PHEULPIN, S. et al. A comparative study of two antimicrobial/antiinflammatory formulations in the treatment of canine otitis externa. **Veterinary Dermatology**, v.16, n. 4, p.299-307, 2005.

SOTIRAKI, S.T.; KOUTINAS, A.F.; LEONTIDES L.S. et al. Factors affecting the frequency of ear canal and face infestation by *Otodectes cynotis* in the cat. **Veterinary Parasitology**, v. 96, n. 4, p.309-315, 2001.

TATER, K.C.; SCOTT, D.W.; MILLER, W.H. et al. The cytology of the external ear canal in the normal dog and cat. **Transboundary and Emerging Diseases**, v.50, n. 1, p.370-374, 2003.