

Evaluation of Owner Compliance with Topical Treatment of Acute Otitis Externa in Dogs: A Comparative Study of Two Auricular Formulations.

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ABSTRACT

Objectives: This study compared owner compliance with two ear treatments: Surolan® (Janssen) 3-5 drops twice daily for 7 days, or Easotic® (Virbac), a pump application, once daily for 5 days.

Animals and Methods: Forty-two dogs with otitis in France and Germany were randomly assigned to receive Surolan® or Easotic®. Each product vial was weighed before and after the study on a precision balance to evaluate the doses actually given. In addition, the owners were asked to answer to a preset phone questionnaire.

Results: The mean ratio: number of doses actually administered/number of doses prescribed, was 1.06 with Easotic® and 0.8 with Surolan®. The ratio was less variable in the Easotic® group (Standard Deviation=0.34, Coefficient of Variation=32%) than in the Surolan® group (SD=0.68, CV=85%). The variance of the ratio was significantly different between the groups (0.13 vs 0.47, $p=0.0081$). Only 10% of owners stated they were able to count exactly

the number of Surolan® drops. More owners in the Easotic® group (100%) than in the Surolan® group (78.9%) positively rated the product frequency of use ($p=0.0424$ between the groups). More dogs were subjectively rated by veterinarians as having considerably improved after treatment with Easotic® ($p=0.0033$ between groups).

Clinical significance: Data from this study suggest that a simplified dosing regimen and method of administration improved owner treatment compliance in canine otitis externa.

INTRODUCTION

Otitis externa is a frequent condition in dogs, with an incidence of 8.6%, according to an epidemiological survey.¹ Clinical signs consistent with otitis externa are pruritus of the ear or face, associated with congestion and swelling of the auditory canal, and purulent auricular discharge or excessive wax.¹

The label treatment duration of most veterinary topical ear formulations on the market is 7 days for acute otitis, while treatment may be prolonged in more chronic cases. Topical treatment needs to be properly carried out for optimal efficacy. Ear medi-

cations may prove difficult to administer by owners, especially when the auricular condition is painful for the dog and when the treatment must be performed twice daily. Achieving good restraint of the dog while counting the exact number of drops required by the veterinarian's prescription is challenging, and the owner may become discouraged before the end of the treatment period, leading to poor compliance and reduced therapeutic efficacy. It is a well-known problem in veterinary medicine that is often related to the complexity of the therapy.²

Recently, a topical ear formulation has been made available in veterinary medicine that is dosed by a pump mechanism delivering a single correct label dose of the product through a flexible cannula each time pressure is applied to the head of the dispenser (Easotic[®], Virbac, Carros, France). It is a once daily 5-day label dosing regimen product proven to be persistence at therapeutic concentrations in the ear canal for several days after treatment cessation. It contains antimicrobial (gentamicine sulfate and miconazole nitrate) and anti-inflammatory (hydrocortisone aceponate) components (European Medicines Agency registration dossier 2009³), and its efficacy in infectious otitis externa was previously demonstrated in dogs.⁴

Accordingly, the aim of this study was not to assess Easotic[®] efficacy, but to demonstrate if the pump mechanism with the 5-day label dosing regimen is able to improve owner compliance compared to a standard drop-dose formulation.

In this study, owner compliance with the administration of this new pump auricular formulation administered according to the instructions was compared with that of a reference drop-dosed auricular suspension, Surolan[®] (Janssen-Cilag, Issy-Les-Moulineaux, France), applied as recommended twice daily for 7 days.

ANIMALS, MATERIALS, AND METHODS

Inclusion and Exclusion Criteria

Dogs of various breeds presenting to the veterinarian for bilateral acute otitis externa were selected to participate in the study. Bilateral otitis externa was defined as the presence of clinical signs of inflammation (erythema, swelling, exudate, ulceration/erosion, and malodor) in both ear canals, as evaluated by otoscopy. Absence of ongoing ear mite infestation was evaluated by the physician. Dogs presenting with otic foreign bodies, hyperproliferation of the ear canal walls, occlusive masses, ruptured tympanic membranes or poor general health were not included in the study. None of the dogs had received any treatment in the 7 days preceding the study. Post-inclusion withdrawal criteria were administration of a concomitant treatment, onset of an unrelated disease likely to affect the dog's behavior or any deviation from the study protocol.

Products

Easotic[®] (Virbac, Carros, France) is a 10mL-multidose dispenser allowing both ears of one dog to be treated over 5 days. The prescribed label dose is 1mL (corresponding to one press on the pump) once daily whatever the size of the dog. The suspension contains hydrocortisone aceponate (1.11mg/mL), miconazole nitrate (15.1mg/mL), and gentamicin sulphate (1505 IU/mL).

Surolan[®] (Janssen-Cilag, Issy-Les-Moulineaux, France) is a 15mL dropper vial, recommended per label to be applied as 3 to 5 drops of the suspension per ear twice daily for at least 7 days. The suspension contains prednisolone acetate (5 mg/mL), miconazole nitrate (23.0 mg/mL), and polymyxin sulphate (5,500 IU/mL).

Study design and schedule

The study was conducted as a randomized parallel design consisting of a non-blinded multisite comparative field trial in France and Germany. At each of the seven participating veterinary practices, dogs complying with the inclusion and exclusion criteria were randomized to one of two treatment groups: Easotic[®] or Surolan[®].

At the initial inclusion visit (V1), the veterinary investigator showed the owner

how to use the product by performing the first treatment, then gave instructions for subsequent administrations that were done at home by the owner using a different vial of the same product. At completion of the treatment (corresponding to visit V2, 5 days for the Easotic® group, 7 days for the Surolan® group), the owner brought back the dog and the used product vial to the investigator. At visits V1 and V2, the veterinarian filled in a case report form.

In the 2 weeks following the study, the owner was interviewed by the monitor of the trial over the phone to answer a preset questionnaire. Throughout the study period, the owner was not informed of the real goal of the study (evaluation of owner compliance), but detailed information about this was given during the interview over the phone, along with the possibility to withdraw from the study afterwards. No owner decided to withdraw her or his consent.

Determination of compliance

Based on the weight of the vials

Before and after completion of the study, each vial of product was accurately weighed at the Laboratory of Analysis of Lattes (Lattes, France), using a precision balance. The weight of the vial after use by the veterinarian at the inclusion visit (π) enabled the weight of the first dose (w) to be determined by subtraction from the initial weight of the same vial before use (P_i). The weight of the vial used by the owner at the end of treatment (p_o) enabled the exact quantity of product used by the owner to be determined (Q) by subtraction from the initial weight of the vial before use (P_o). The number of doses actually administered by the owner (D) was calculated as:

$$D=(Q/w).$$

The ratio of the actual number of doses administered (D) / the number of doses prescribed (8 doses in the Easotic® group and 26 doses for the Surolan® group), defined as the compliance ratio, was calculated for each case.

Based on owner feedback

Over the phone, the owners were asked about the quantity and frequency of product actually applied, and how many doses were missed. They were also interviewed about their understanding of their dog disease.

Opinion of the owner on the product

Over the phone, the owners were asked open questions relative to the benefits and drawbacks of the product, satisfaction with duration and frequency of treatment, and overall satisfaction with treatment.

Opinion of the investigator on the product

At visit V1, the veterinarians recorded in the case report forms their own evaluation of product ease of use, as well as the type and severity of the otitis. At visit V2, they gave their opinion about the owner reliability in performing properly the prescription.

Statistical analysis

Descriptive statistics were used to report animal characteristics recorded by the veterinarians, as well as the opinions of the owners on the treatment duration and frequency of use.

The mean and standard deviation (SD) of the compliance ratio, as well as its variance, were calculated for each group using the software package R (www.r-project.org). The coefficient of variation (CV) was calculated as mean/SD. Owners were considered as objectively compliant when the compliance ratio was between 0.7 and 1.3 ($\leq 30\%$ difference between dose actually administered and dose prescribed).

Fisher's exact tests were performed for between-group comparisons of qualitative parameters such as animal gender, severity of otitis, owner and investigator opinions, and proportion of owners reporting missing doses.

An F-test was performed to compare the variance of the compliance ratio between the two treatment groups.

RESULTS

Sample Size

Forty-two dogs, 21 in each group, were recruited over the study period. The sex

Table 1. Animal characteristics at inclusion in the study.

Parameter	Easotic® (n=21)	Surolan® (n=21)	Between-group comparison (P-value)
Dog gender			
Female	10 (47.6%)	11 (52.3%)	1
Male	11 (52.3%)	10 (47.6%)	
Type of otitis*			
Erythemato-ceruminous	15 (81%)	16 (85.7%)	1
Purulent	4 (19%)	3 (14.3%)	
Severity of otitis			
Slight	4 (19%)	6 (28.6%)	0.1947
Moderate	14 (66.7%)	8 (38.1%)	
Severe	3 (14.3%)	7 (33.3%)	

* Two missing data in each group.

ratio was balanced in both groups (Table 1). Twenty-six breed were represented, including most frequently Poodle or Poodle mix (11.9%), German shepherd (7.1%), Labrador retriever, and Labrador retriever mix (7.1%), Teckel (7.1%), Boxer (4.8%), Cavalier King Charles (4.8%), French Bulldog (4.8%), Griffon (4.8%), Springer spaniel and Springer spaniel mix (4.8%), and Yorkshire Terrier (4.8%). Other breeds were minority represented (1 dog each ie, 2.4%): Basset Fauve De Bretagne, Beagle, Bichon, Brittany Spaniel, Bull Terrier, Cocker spaniel, English Setter, French Spaniel, Golden Retriever, KorthalsLeonberg, Mixed breed, Newfoundland, Pit bull, Shi Tsu, and Welsh Terrier.

Two dogs in each group (four dogs) could not be included in the calculation of the compliance ratio because of deviation to the protocol procedures. In addition, one owner in the Surolan® group refused to answer the questionnaire and his opinion could not be recorded, despite the fact that he did not withdraw his content for including his dog's results in the study.

Therefore, the analysis of the compliance ratio was done on 19 dogs in each group and the analysis of owner opinions was performed with 21 answers in the Easotic® group and 20 in the Surolan®

group.

Types and Severity of Otitis at Presentation

The great majority of dogs in both groups presented for erythemato-ceruminous otitis. There was no significant difference between the groups for the severity of otitis at inclusion (Table 1).

Compliance

Based on Owner Feedback

One owner reported one a missed dose with Easotic® and two owners reported that they

Figure 1. Box plots of the compliance ratio (number of doses actually administered by the Owner/ number of doses prescribed by the veterinarian).

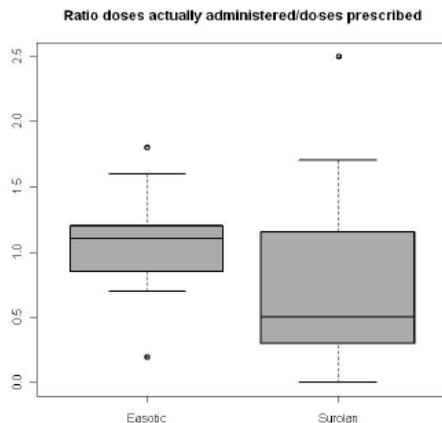


Table 2. Number of owners with objective measurement of compliance (compliance ratio) outside the normal range and possible reasons identified.

Non-compliance issue	Easotic® N=19	Surolan® N=19
Nb (%) of non-compliant owners: Compliance ratio outside the normal range (<0.7 or >1.3)	4/19 (21.1%)	15/19 (78.9%)
Possible reasons for lack of compliance		
Missed doses reported by non-compliant owners	0/4	2/15
Difficulty in applying the right dose reported by non-compliant owners*	0/4	14/15
Wrong frequency or duration of treatment applied by non-compliant owners	0/4	1/15
Misunderstanding of the medical condition being treated** by non-compliant owners	2/4	5/15
Non-compliant owners subjectively rated as moderately reliable by the veterinarian	1/4	3/15†

*owner unable to apply one pressure (Easotic® group) or to count exactly the number of drops prescribed by the veterinarian (Surolan® group); **owner unable to name the medical problem for which the dog is being treated (otitis); † One investigator has no idea.

missed between one and three doses of Surolan®. However, these statements did not necessarily correlate with wrong compliance ratio. There was no significant difference between the treatments for the number of doses missed according to owners' reporting ($p=0.4615$).

Based on weighing of vials

The compliance ratio in each group is represented by box plots in Figure 1. With Easotic®, the compliance ratio ranged from 0.2 to 1.8, being close to 1 (0.7-1.3 reference range) for 15 owners (78.9%). With Surolan®, the ratio ranged from 0 to 2.5, and only 4 owners (21.1%) had a compliance ratio close to 1 (0.7-1.3 reference range; Table 2).

A significant difference was detected between treatments for the variance of the compliance ratio ($p=0.0080$). The compliance ratio with Easotic® (1.06 ± 0.35) was less variable (coefficient of variation CV:

33%) than that with Surolan® (0.8 ± 0.68 , CV: 85%) (Figure 1).

Possible Reasons for Lack of Compliance

The possible reasons for lack of compliance have been sought through the owner questionnaire and the investigators' opinion (Table 2).

Wrong Frequency or Duration of Treatment Applied by Non-compliant Owners

Over the phone, the frequency and duration of administration stated by Owners was wrong in only three cases. However, it was related to a low compliance ratio results for only one Owner in the Surolan® group and no owner in the Easotic® group.

Difficulty in Applying the Right Dose Reported by Non-compliant Owners

Among the 15 owners presenting a compliance ratio outside the reference range in the Surolan group, 14 found it difficult to apply the right dose.

Among the four owners presenting a compliance ratio outside the reference range in the Easotic group. None found it difficult to apply the right dose.

Misunderstanding of the Medical Condition Being Treated by Non-compliant Owners

The dog disease (otitis externa) was not understood in 2/4 owners with a compliant ratio outside the reference range in the Easotic® group and in 5/15 owners with a compliant ratio outside the reference range in the Surolan® group.

Reliability of the Owner According to the Investigator

One of the non-compliant owners (based on compliant ratio) was deemed as not reliable to perform properly the treatment according to the Investigator in the Easotic® group, while the unreliability concerned 3/15 owners in the Surolan® group. In that group, for one owner, the Investigator stated that he has no idea of the owner reliability.

Opinion of the Owners on Product Features

Product Features Appreciated by the Owners

More owners were satisfied with at least one characteristic of the product as related to compliance with Easotic® or with Surolan® (Table 3) (p=0.0448).

The most appreciated features with Easotic® included were ease of use (27.3%), efficacy (24.2%), and accurate dosing (18.2%).

One owner (3%) did not find any positive aspect in the Easotic® product.

The Surolan® features most appreciated by owners were efficacy (23.8%) and ease of use (4.8%). Six owners (30%) did not find any positive aspect in the Surolan® product.

Product Features Disliked by the Owners

Nearly one owner in five disliked at least one thing in Easotic®, as compared to half with Surolan® (Table 3; p=0.0516).

The Easotic® features not appreciated by

Table 3. Subjective assessment of owners and veterinarians on product features related to compliance.

Parameter	Easotic®	Surolan®	Between-group comparison (P-value)
Owners opinion	n=21	n=20	
Satisfied with at least one positive feature of the product as relates to product use	20 (95.2%)	14 (70%)	0.0448
Dissatisfied with at least one negative feature of the product as relates to product use	4 (19%)	10 (50%)	0.0516
Satisfied with duration of treatment	v21 (100%)	17 (85%)	0.1069
Satisfied with frequency of treatment	21 (100%)	15 (75%)	0.0424
Globally satisfied with the product	21 (100%)	17 (85%)	0.1069
Veterinarians opinion	n=21	n=21	
Satisfied with product easiness of use	19 (90.5%)	9 (45%)*	0.0025

* One opinion missing (n=20)

owners included: nothing (77.3%), a slightly excessive dose (4.5%), strong odour (4.5%), greasy deposits at the ear canal opening (4.5%), absence of protective cap on the cannula (4.5%), and inability to check the amount of suspension administered in the ear canal (4.5%).

The Surolan[®] features disliked by owners included: nothing (45.5%), inaccurate dosing (22.7%), unsuitable cannula (9.1%), lack of efficacy (4.5%), not easy to use (4.5%), inadequate consistency of the suspension (9.1%), and greasy deposits at the ear canal opening (4.5%).

Only 10% (2/20) of owners stated that they were able to count exactly the number of Surolan[®] drops prescribed by the veterinarian.

Opinion of the Owners on the Frequency and Duration of Treatment

More owners were happy with the once-daily use and 5-day duration of treatment of Easotic[®] than with the twice-daily use and 7-day treatment regimen of Surolan[®] (Table 3; $p=0.1069$ and $p=0.0424$ for duration and frequency of administration respectively).

Global Satisfaction of the Owners with Treatment

Good overall satisfaction rates were observed in both groups, with no significant difference between the groups (Table 3; $p=0.1069$).

Opinion of the Veterinarians on Product Ease of Use

The great majority of veterinarians found Easotic[®] easy to use (Table 3), except one difficulty in priming the pump for one veterinarian and in another case the noise associated with the product administration seemed to scare the dog.

Surolan[®] was found easy to use by a minority of veterinarians (Table 3). Most of the time difficulty with product administration was related to an inability to count the exact number of drops.

Veterinarians rated Easotic[®] significantly more favorably than Surolan[®] in terms of ease of use (Table 3; $p=0.0025$).

DISCUSSION

In this field trial, a new ear formulation delivered by a pump delivery system was compared with a reference ear formulation delivered by a drop-dosing dispenser in terms of owner compliance with the prescribed treatment of acute otitis externa. Clinical findings are limited in this study because it focused on client compliance.

Compliance of the owners with the dose prescribed by the veterinarian was objectively assessed by weighing the product before and after treatment. This method gave an accurate indication of the total quantity of product actually used by the owner, though no information was provided on the number of days when the correct dose was administered, and it is not known whether or not the doses were applied on schedule.

The latter information can only be obtained using MEMS (Medication Event Monitoring System)-equipped containers, with electronic monitoring caps. MEMS are used in human medicine to assess patient adherence to the oral treatment of severe and chronic diseases (hypertension for example), with significant economic and public health impacts.⁵ They have been used in veterinary medicine to assess client compliance with the administration of oral antibiotics to dogs,^{6,7} but the devices are large, expensive, and difficult to use, and so would not have been suitable for the practical evaluation of topical ear formulations tested in their original dispensers. The ratio of the total number of doses actually administered by the owner / the total number of doses prescribed by the veterinarian was used to compare owners' adherence to treatment with the two products, since Easotic[®] and Surolan[®] have different label regimens. A margin of tolerance from 70% to 130% of the total dose prescribed was deemed acceptable, to take into account variability in bottle and dose weight measurements. According to these cut-off values, most owners (15/19) were compliant with the prescribed Easotic[®] treatment schedule, whereas a minority of owners (4/19) complied with the Surolan[®]

label treatment regimen. In addition, a higher variability in the compliance ratio was observed in the Surolan® group, suggesting better ability of the owners to follow the Easotic® prescription.

Differences between groups cannot be explained by factors such as the type and severity of otitis (reaction of the animal to product application), since these parameters were comparable between the groups at baseline. Reduced compliance by the clients of a veterinary practice may result from perceived complexity of the treatment, misunderstanding of the instructions provided by the practitioner, lack of motivation or forgetfulness, and insufficient follow-up. Patient education is recommended in human medicine to improve compliance and the same is true for pet owners.⁸ Few studies are available in the veterinary literature that objectively evaluate owner compliance with medication in dogs. All of them refer to oral antimicrobial drug use, not to topical formulations.^{6,7,9-11}

In this study, the pre-set delivery system allows application of the exact therapeutic daily dose through the cannula with one pump application, and the label treatment is simple and short. Conversely, the main reason identified for owner non-compliance in the control group (Surolan®) was related to owner difficulty in counting the exact number of drops required twice daily. It can indeed be challenging at times to handle the dog while at the same time making sure that the right amount of suspension is delivered into the ear canal, especially if the condition is painful or if the dog is reacting to the product administration.

The compliance rate determined from client self-reporting in the questionnaire was much higher than that assessed by bottle weighing. Such a discrepancy between owner subjective self-evaluation and an objective measure of compliance is in agreement with results of other veterinary studies on patient compliance.^{7,10} It may be explained in the present case by under-reporting of deviations or, in the control product group,

by inaccuracy of drop counting.

Despite the fact that no significant difference was detected between the two treatments for owner global satisfaction, more owners were satisfied with the Easotic® treatment frequency and subjectively appreciated at least one positive aspect of product use. Veterinarians were also more frequently satisfied with Easotic® ease of use as compared with Surolan®. Ease of use of medications is one important element in improving patient compliance, and hence treatment efficacy.¹²

The study presents some limitations. First, the amount of product that has come out of the bottle does not necessarily correlate with the amount of product that has entered the external ear canal. But the owner questioning also aimed to crop details about administration and its difficulty including product wasting, and no report of repeated administrations because of application failure was recorded.

The study was not blinded, however, the objective of the study was blinded for the owner, and since the main results were based on the owner observance and not on a subjective evaluation, it may reasonably be thought that the absence of blinding had no impact on the results obtained from the owner.

The accurate diagnosis of infection was not always performed by laboratory methods. However, the study is not an efficacy trial and the inclusion criteria required dogs with no mites infection and no atopic otitis, since the first indication is not included in the recommendations for use of the product and the latter required a concomitant treatment. The origin of the otitis is unlikely to impact the owner observance, as long as the dog condition (general health and behavior) was deemed to be normal. The efficacy of Easotic under similar field conditions was already shown in a previous clinical trial.⁴

Despite these limitations, it may be considered that all efforts were made to avoid bias to assess Owner compliance under field conditions of use.

In conclusion, data from this study suggest that use of an antibiotic-antifungal-corticoid ear formulation delivered by a constant-dose pump delivery system improves client compliance with the treatment of acute otitis externa in dogs, as compared to a reference antibiotic-antifungal-corticoid ear formulation administered as drops. Reduction of variability in dosing over time and between subjects should be beneficial for the treatment of infectious otitis in dogs, since effective therapy of this condition depends primarily on the good performance of the daily topical treatment by owners at home. The efficacy of the product in infectious otitis has been successfully demonstrated in previous studies.⁴

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