

Efficacy of a Formulation Containing Imidacloprid and Permethrin Against Naturally Acquired Ectoparasite Infestations (*Ctenocephalides felis*, *Cheyletiella parasitovorax*, and *Listrophorus gibbus*) in Rabbits

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ABSTRACT

The purpose of this study was to evaluate the efficacy of a topical formulation containing imidacloprid and permethrin for eradication of a patent flea (*Ctenocephalides felis*) and mite (*Cheyletiella parasitovorax* and *Listrophorus gibbus*) infestation in rabbits. Sixteen adult rabbits from a rabbit husbandry were enrolled in the study. Rabbits were treated with 40 mg imidacloprid and 200 mg permethrin dermally as spot-on on Day 0. No other treatment or environmental decontamination was performed during the trial. Prior to treatment followed by 14, 28, and 42 days post treatment, all rabbits were

combed and examined for fleas, flea feces, mites, and their developmental stages. Clinical signs had subsided by Day 14 in all rabbits and no signs of recurrence were apparent in the following weeks. No fleas or mites, including developmental stages, were captured and no flea feces were found on Days 14, 28, and 42. No adverse reactions were observed. Under the conditions of our study, topical formulation of imidacloprid and permethrin was a practical and well-tolerated means of treatment for flea infestation in rabbits.

INTRODUCTION

Flea and mite infestations are a common cause of skin disorders and reason for consultation in small animal practices. Fleas and mites cause irritation in rabbits as well as dogs and cats. Rabbits can be readily

infested by the cat flea *Ctenocephalides felis* from dogs and cats; by *Spilopsyllus cuniculi* after contact with wild rabbits^{1,2}; and also by *Pulex irritans*, *Echidnophaga gallinaceum*, or *Nosopsyllus fasciatus*.³ Clinical features vary from asymptomatic to severe hypersensitivity reactions with restlessness, alopecia from scratching and biting resulting in a pruritic papular dermatitis.^{3,4} *Cheyletiella parasitovorax* and *Listrophorus gibbus* are commonly found on rabbits and are thought to be a normal commensal.^{3,5}

The responsibility for the care of companion animals including exotic pets other than dogs and cats also falls to the animal practitioner, and while dogs and cats remain the main pets throughout Europe and North America, there is an increase in ownership of pets other than canine or feline. Since there are few substances licensed for use on exotic pets, veterinary surgeons often turn to off-label use of products that are available for the treatment of other species.⁶

A new dermal product has been developed containing imidacloprid and permethrin (Advantix[®], Bayer AG, Germany), which is administered as a topical application to the skin at a single site on dogs. No information is available on the efficacy of this preparation to control rabbit flea infestation. The present clinical study was conducted to evaluate the efficacy and tolerance of a spot-on formulation with imidacloprid and permethrin in the treatment of rabbits naturally infested with *C. felis*, *C. parasitovorax*, and *L. gibbus*.

MATERIALS AND METHODS

Sixteen adult rabbits (14 female, 2 male) of the breed "Sachsendgold" with a natural *C. felis*, *C. parasitovorax*, and *L. gibbus* infestation were enrolled in this clinical study. All rabbits were from the same rabbit husbandry in Rodgau/Jugesheim near Frankfurt/Main (Germany) and kept in an enclosure outdoors during the day and in cages indoors over night and during the treatment period. Ages ranged from 6 months to 1 year with a mean age of 9

months. On Day 0, all animals were weighed individually. Body weight (BW) of the rabbits ranged from 2.4 to 4 kg BW with a mean BW of 2.9 kg.

Treatment

Each rabbit received one spot-on treatment on study Day 0. Dermal application was performed using 0.4 mL of a topical solution containing 40 mg imidacloprid and 200 mg permethrin (Advantix[®], Bayer AG, Germany) at the base of the neck. Due to animal welfare within this clinical field trial with heavily flea- and mite-infested animals, a placebo treatment group was not enrolled. Because of the comparatively small number of patients and in order to achieve more representative results, a positive control treated with another insecticide/acaricide was not included. No other treatment or environmental decontamination was performed during the trial. The success of the therapy was assessed by clinical as well as parasitological examination.

Clinical Examination

General health of all treated animals was observed daily by the husbandry owner from Day 0 for the duration of the study, except for Days 14, 28, and 42 when a detailed clinical check-up was conducted by the veterinarian. At these particular assessment dates, the general condition of the haircoat with respect to appearance of scaling and crusting or flea feces was judged for each rabbit. During the course of the trial, evaluations of the current state and observed side effects were recorded.

Parasitological Examination

On Days 0, 14, 28, and 42, all rabbits were thoroughly combed craniocaudal with a stainless steel fine-toothed flea comb (12 points/cm) 4 times (2 times each right and left paramedian sight) on the dorsal and on the ventral trunk, respectively. The comb was pulled through the haircoat from the neck until the origin of the tail dorsally, and from the neck until the inguinal region ventrally. Captured specimens were counted

and afterwards collected in small plastic containers and preserved frozen until microscopic examination and identification. The flea species determination was based on microscopic examination; the nomenclature of Peus (1938)⁷ and Pospischil (2002)⁸ were used for identifying flea species. By combing, obtained hair and skin samples were examined microscopically for detection and quantification of mites and their developmental stages. Detected fleas and mites were evaluated for each patient by scoring from absent (-), 1-3 specimens (+), 4-6 specimens (++), or >6 specimens (+++) on Days 0, 14, 28, and 42. With respect to appearance of flea feces in the hair coat, this was recorded by scoring from absent (-), few (+), moderate (++), or plenty (+++) on Days 0, 14, 28, and 42.

RESULTS

Owners reported about reduced appetite and increasing restlessness in their animal husbandry over the last weeks. Furthermore, a number of adult fleas and small crumbs of flea feces in the hair coat of some rabbits were observed. All fleas sampled from the rabbit's haircoat in this trial were *C. felis*. The rabbits showed mild scaling and crusting on the whole body; 2 rabbits exhibited ventral alopecia and 1 rabbit exhibited dorsal alopecia on Day 0 (Figure 1). On Day 14, the owners reported that the general condition of all rabbits (Figure 2) improved

Figure 1. Dorsal alopecia of breeding rabbits naturally infested with *Ctenocephalides felis* prior to treatment.



remarkably. Moreover, the appetite returned for all treated animals. Clinical signs were absent by Day 14 in all 16 rabbits and no signs of recurrence were apparent on assessment Days 28, 42, and in the following weeks. The animals showed a bright haircoat without any scaling and crusting or crumbs of flea feces starting from Day 14. No fleas or mites, including their developmental stages, were captured and no flea feces were found on combing Days 14, 28, and 42, which appeared to correlate with clinical improvement.

The number of fleas, flea feces, and mites recovered from the rabbit's haircoat were documented for each patient on the assessment days (0, 14, 28, and 42). For each assessment day within the study, the parasitological status was assessed in order to specify the efficacy of the used parasiticide (Tables 1 and 2). As shown in Table 1, fleas were found in all animals (7/16: +, 2/16: ++, 7/16: +++) on Day 0, but had declined on Day 14. Seven of 16 rabbits harbored few fleas right from the start, and all showed flea feces; also, mites were found in their hair coat. All 16 rabbits were parasitized by fur mites (+ to +++), *L. gibbus*, in conjunction with their numerous eggs fixed on the hairs. On 1 rabbit, a *C. parasitovorax* infestation (Figure 3) was observed. The check-up for *Psoroptes cuniculi* by collecting epidermal debris from both auricular areas and the external ear

Figure 2. Cured rabbits from Figure 1 on trial Day 42 after topical application of the imidacloprid/permethrin spot-on combination.

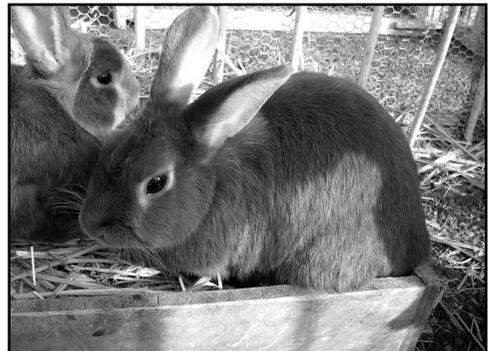


Table 1. Parasitological Examination of Rabbits With Naturally Acquired Ectoparasite Infestation Before and After Treatment With an Imidacloprid/Permethrin Combination With Respect to Appearance of Flea Feces.

Evaluation of Flea Feces in the Rabbit's Haircoat	Number of Rabbits With or Without Flea Feces*			
	Day 0	Day 14	Day 28	Day 42
Absent (-)	0	16	16	16
Few (+)	11	0	0	0
Moderate (++)	1	0	0	0
Plenty (+++)	4	0	0	0

*Treatment (Day 0) and assessment days (Days 14, 28, and 42).

Table 2. Parasitological Examination of Rabbits With Naturally Acquired Ectoparasite Infestation Before and After Treatment With an Imidacloprid/Permethrin Combination With Respect to Appearance of Adult Fleas and Mites (flea and mite counts are summarized)

Flea and Mite Counts	Number of Rabbits With or Without Flea Feces and Mites*			
	Day 0	Day 14	Day 28	Day 42
0 (-)	—	16	16	16
1-3 (+)	7	—	—	—
4-6 (++)	2	—	—	—
> 6 (+++)	7	—	—	—
Efficacy (%)	—	16/16 (100)	16/16 (100)	16/16 (100)

*Treatment (Day 0) and assessment days (Days 14, 28, and 42).

Figure 3. *Cheyletiella parasitovorax* from one of the multiparasite-infested rabbits.



canal for microscopic examination proceed negative. Neither fleas (dead or alive) nor flea feces in any rabbit were detected on assessment Days 14, 28, and 42. All mites (*L. gibbus* and *C. parasitovorax*) as well as their developmental stages were absent on Days 14, 28, and 42. Thus, efficacy of the imidacloprid/permethrin spot-on formulation rated 100% at these points of time, accordingly. The spot-on was well tolerated systemically and locally. Administration regions for the spot-on compound on the base of the animal's neck did not show any erythematous or pruritic irritations.

DISCUSSION

Fleas and mites can infest rabbits whether or not the rabbits share the household or environment with other pets, such as dogs and cats. Except for wild rabbits parasitized from *S. cuniculi*, flea infestation is seen predominantly in large agricultural or breeding rabbit husbandries than in single pet rabbits. However, flea infestation in pet rabbits is recorded frequently in cases of multi-pet households, when rabbits and cats or dogs share a household. Mite infestations normally occur in any rabbits irrespective of their kind of husbandry. Although our study does not allow us to conclude how the flea infestation is usually acquired, the fact that several stray cats are frequently found in the neighborhood near the husbandry may be seen as a constant source of infestation with cat fleas. After capturing 3 of those roaming cats, detailed examinations revealed a severe flea infestation with *C. felis* in all cases. Therefore, insecticidal treatment of cats in the environment is essential for ultimate solution of this ectoparasitic problem. The investigations by Beck et al⁹ confirm the results from previous studies that *C. felis* is the predominant flea species found on dogs and cats during all seasons of the year. The reason for more cats being infested by

cat fleas than dogs is not resolved by the data, but may be due to different behaviors between dogs and cats. A possible explanation is that felines usually roam more freely than dogs and may therefore have more opportunities to interact with other cats or other free-living animals, including rabbits. Moreover, cats frequently have resting places away from their permanent homes, where external parasites may persist.¹⁰ The climatic and environmental conditions in households,¹¹ orchards, and the open countryside are important for the dynamics of flea populations. Some authors quantified the probability of transmission of fleas from the environment to the animal and emphasized its fundamental importance for the design and implementation of effective control strategies.¹²⁻¹⁴ Infestations with *S. cuniculi* appear where there is contact with wild rabbits.¹² According to Wall and Shearer,³ *Pulex irritans*, *Echidnophaga gallinaceum*, and *Nosopsyllus fasciatus* can infest rabbits as well. The flea infestations in the present field study were accompanied by fur mite (*L. gibbus*) infestations in all 16 rabbits. *Listrophorus gibbus* is thought to be a commensal ectoparasite, asymptomatic in normal healthy adult animals. However, when heavy infestations occur or where there is an underlying disease, alopecia, moist dermatitis, mild scurf, and pruritus may develop.⁵ Furthermore, 1 patient harbored *C. parasitovorax*. A common clinical description of *Cheyletiella* is "walking dandruff," describing the effect of the migration of the relative large mites amongst the numerous skin debris into the coat resulting from a heavy infestation. Other signs are variable and include pruritic dermatitis and alopecia.¹⁵ *Listrophorus gibbus* and *C. parasitovorax* are considered to be species specific. The appearance of the studied 3 different arthropod species observed in a husbandry of breeding rabbits demonstrates the need for effective ectoparasite control to maintain the animal's well-being.

In this trial, the spot-on formulation containing imidacloprid and permethrin was 100% effective from the beginning against

naturally acquired infestations of *C. felis*, *C. parasitovorax*, and *L. gibbus* in rabbits. Although there was no control group, the treatment regimen appeared effective and tolerable in the clinical control of flea and mite infestations. A lack of licensed antiparasitics for this indication in rabbits in most countries requires an off-label use of adequate pharmaceuticals. The simple dosing protocol used, with a topically administered spot-on formulation at the base of the rabbit's neck, facilitates owner compliance with the treatment protocol. The spot-on application is in contrast to traditional routes of administration, like bathing or powdering. The latter require more applications and a higher incidence of recurrence of those administrations are much more time-consuming and laborious; thus, owner compliance favors spot-on applications. The results from Hutchinson et al¹⁶ indicate that imidacloprid as mono-substance is a good alternative for the flea control in artificially infested rabbits. After topical administration of the substance, imidacloprid is rapidly distributed over the animal's skin within 1 day after application. Imidacloprid was safe when used on rabbits and eliminated resident flea populations. The 0.4-mL dose was highly effective and gave substantial protection. This is in accordance to the results of Jacobs et al,¹ who evaluated efficacy of imidacloprid on rabbits naturally and experimentally infested with the cat flea. In the UK, imidacloprid (Advantage[®], Bayer AG, Germany) with a dosage of 10 mg/kg BW is officially licensed for flea control in rabbits, except for animals younger than 10 weeks. Results of another study¹⁷ revealed that a single topical application of imidacloprid can completely eliminate fleas from domestic rabbits naturally infested with *C. felis* within 2 days. In addition, a high residual impact for at least 1 week post treatment was observed. Corresponding to another report,¹⁸ a single spot-on treatment of selamectin at a dose rate of 18 mg/kg BW is recommended for flea treatment in rabbits with a repeat therapy in 30 days if required. Hughes² recommends therapy with 15 mg

selamectin for rabbits weighing less than 2.3 kg and 45 mg for those weighing more than 2.3 kg, with a second application after 1 month to kill emerging larvae of *C. parasitovorax*, and *L. gibbus*. The use of fipronil against fleas or mites on rabbits has never been recommended or approved by the manufacturer. In the literature, reports of adverse reactions including deaths due to fipronil are given when applied to rabbits.¹⁹

Under the conditions of our trial, the topical formulation containing imidacloprid and permethrin resulted in a complete reduction in the prevalence of clinical signs associated with flea and mite infestation in the treated rabbits. Advantix® was well-tolerated by all infested rabbits without any side effects. The results indicate that imidacloprid plus permethrin at a single dosage of 40 and 200 mg/kg BW, respectively, topical applied is an effective and appropriate choice for the ectoparasite control in rabbits.

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