Efficacy of afoxolaner plus milbemycin oxime and afoxolaner alone as treatment for sarcoptic mange in naturally infested dogs

Camilo Romero-Núñez, Linda G. Bautista-Gómez, Galia Sheinberg, Alberto Martín-Cordero, Ariadna Flores-Ortega, Rafael Heredia-Cárdenas

Abstract

Sarcoptic mange is a pruritic, contagious, ectoparasitic skin disease that affects mammals, including the domestic dog. The objective of this study was to evaluate and compare the efficacy of afoxolaner plus milbemycin oxime (NexGard Spectra) and afoxolaner alone (NexGard) as treatments for sarcoptic mange in naturally infested dogs. A total of 142 dogs naturally infested with *Sarcoptes scabiei* were evaluated. The dogs were diagnosed by microscopic examinations of skin scrapings. The dogs were divided into 2 groups: 96 dogs were treated with a combined dosage of 2.50 to 5.36 mg/kg body weight (BW) of afoxolaner and 0.50 to 1.07 mg/kg BW of milbemycin oxime and 46 dogs were treated with 2.50 mg/kg BW of afoxolaner alone. The presence or absence of pruritus and lesions were evaluated using an analogous scale on days 7, 14, 21, 28, and 56 after receiving the treatment. Data obtained were analyzed by Student’s *t*-test (*P* ≤ 0.05). The single oral treatment of afoxolaner plus milbemycin oxime resulted in a significant reduction in pruritus of 87.4% at 28 d after treatment (*P* ≤ 0.05). Resolution of the lesions after treatment was variable, with a significant decrease (*P* ≤ 0.05) observed within the first 14 d, although this parameter continued to improve until the end of the study on day 28, when a decrease of 96% was observed. By the end of the study, a single dose of either the afoxolaner alone or the afoxolaner combined with milbemycin oxime was effective in significantly reducing the signs associated with sarcoptic mange during a 56-day evaluation period.

Résumé

La gale sarcoptique est une maladie cutanée pruritique et contagieuse causée par un ectoparasite qui affecte les mammifères, incluant le chien domestique. L’objectif de la présente étude était d’évaluer et de comparer l’efficacité d’axoloxolaner plus oxime de milbémycine (NexGard Spectra) et l’afloxolaner seul (NexGard) comme traitement pour la gale sarcoptique chez des chiens naturellement infestés. Un total de 142 chiens naturellement infestés avec *Sarcoptes scabiei* furent évalués. Les chiens étaient diagnostiqués par examen microscopique de grattages cutanés. Les chiens furent divisés en deux groupes : 96 chiens furent traités avec un dosage combiné de 2,50 à 5,36 mg/kg de poids corporel (BW) d’axoloxolaner et de 0,50 à 1,07 mg/kg BW d’oxime de milbémycine et 46 chiens furent traités avec 2,50 mg/kg BW d’axoloxolaner seul. La présence ou l’absence de prurit et de lésions furent évaluées en utilisant une échelle analogue aux jours 7, 14, 21, 28 et 56 après avoir reçu le traitement. Les données obtenues furent analysées à l’aide d’un test de *t*-student (*P* ≤ 0.05). Le traitement unique avec de l’afloxolaner plus oxime de milbémycine a entraîné une réduction significative du prurit de 87,4 % au jour 28 après le traitement (*P* ≤ 0.05). La résolution des lésions après le traitement était variable, avec une diminution significative (*P* ≤ 0.05) étant observée au cours des 14 premiers jours, bien que ce paramètre continua de s’améliorer jusqu’à la fin de l’étude au jour 28, alors qu’une diminution de 96 % fut observée. À la fin de cette étude, une dose unique de soit de l’afloxolaner seul ou une combinaison afoxolaner-oxime de milbémycine était efficace à réduire de manière significative les signes associés avec la gale sarcoptique durant une période d’évaluation de 56 jours.

(Traduit par Docteur Serge Messier)

Introduction

Sarcoptic mange in animals, which is caused by the *Sarcoptes scabiei* mite (1), is still a problem in most parts of the world (2). Although mites are largely a host-specific species in their natural range, there are reports of *S. scabiei* infesting diverse hosts, including more than 100 species of mammals, such as dogs, cats, rabbits, ovines, bovines, raccoons, and humans (2,3). *Sarcoptes scabiei* is a permanent obligate ectoparasite that lives and reproduces in the epidermis (4), most notably in sparse hair regions.

Infestations of *S. scabiei* var. *canis*, which causes sarcoptic mange in dogs, are not seasonal and have no age, breed, or sexual prevalence (5). However, animals enduring poor conditions, such as stress, overpopulation, poor nutrition, or immunosuppression, seem to...
be most susceptible to the disease (6). Sarcoptic mange is a pruritic disease with lesions that usually begin in less dense regions of the integument, such as the periocular skin, ear margins, and elbows (7). It can manifest itself via alopecia, scales, scabs, papules and, less often, lichenification and melanoderma (8). Skin damage can occur due to self-trauma secondary to pruritus (9), which allows mites to spread to an increasing proportion of the epidermis (7). Secondary skin infections are also common (9).

Diagnosis is based on clinical history, with a sudden onset of intense itching in one or more localized areas (10). Diagnosis is definitive with microscopic examination of skin scrapings revealing mites, eggs, and the remains of feces (11). As the sensitivity of this test has been shown to be less than 50% (12), the response to treatment is also considered a diagnostic method (13).

Therapeutic options for controlling sarcoptic mange consist of topical products such as selamectin (8) or moxidectin with imidacloprid (14). Medicated baths are usually part of the therapy to control scabies as they reduce the presence of scabs and dead mites and shorten treatment times (8). Subcutaneous ivermectin has also shown a variable response (15,8,16), although some dog breeds show adverse effects (17). A recent therapeutic option for sarcoptic mange in some areas is oral treatment with isoxazolines (18,5), which have demonstrated potent acaricidal and insecticidal activity through a mechanism of binding to neuronal chloride channels activated by gamma-Aminobutyric acid (GABA) and glutamate (19).

Afoxolaner, a molecule belonging to the isoxazole class, has proven to be effective against S. scabiei, showing complete parasitological cure in dogs with sarcoptic mange after monthly oral treatment at the minimum effective dose of 2.50 mg/kg body weight (BW) (20). A chewable formulation that combines afoxolaner with milbemycin oxime, a macrocyclic lactone, has recently been registered to treat and control infestations of fleas, ticks, and infections with intestinal nematodes (21). Although milbemycin oxime is nematocidal, it has also been used in the treatment of sarcoptic mange and has proven useful in therapeutic management of scabies in dogs (22), without adverse reactions in dogs considered potentially sensitive to ivermectin (23). Therefore, the present study was designed to compare the efficacy of afoxolaner plus milbemycin oxime and afoxolaner alone as a treatment in dogs with natural infestation of S. scabiei.

Materials and methods

This study protocol was approved by the Ethics Committee of the Amealcamo University Center of the Autonomous University of the State of Mexico (UAEM142), client-owned dogs from the State of Mexico, Mexico City, and Guadalajara, Mexico were included. The inclusion criteria were dogs of any age, breed, and gender that were positive for S. scabiei on microscopic study and with the prior approval of the owner by a letter of consent. The dogs were considered positive when the skin microscopy showed at least 1 infective form of S. scabiei, which was identified according to the morphology of the American Association of Veterinary Parasitologists (AAVP) guide (24), and with characteristic signs of sarcoptic mange.

During the treatment period, the dogs remained in standard accommodation and were fed a standard diet. All dogs were evaluated on days 1, 7, 14, 21, 28, and 56. The evaluations were made by microscopy, with samples obtained by scraping, and by observing clinical signs of sarcoptic mange, such as erythema, comedones, follicular papules, pustules, scales, scabs, and alopecia. Areas such as the face, head, neck, sternum, chest, groin, abdomen, back, sides, front, rear end, perianal, perigenital, and tail were evaluated and each sign assigned a value of 0 (none), 1 (light), 3 (moderate), and 6 (severe), with a maximum value of 864 points. The level of pruritus was evaluated using a scale of 0 to 10, depending on its intensity. The evaluations of the dermatologic and pruritic lesions were carried out by the same person every day, for each dog.

A total of 142 dogs took part in this study. The dogs were divided into 2 groups. Group 1 consisted of 96 dogs and group 2 consisted of 46 dogs. On day 1 (time of positive skin scrapings), the dogs in group 1 were treated orally with a combination of 2.50 to 5.36 mg/kg BW of afoxolaner and 0.50 to 1.07 mg/kg BW of milbemycin oxime in a chewable tablet (NexGard Spectra; Mérial, Lyon, France). Dogs in group 2 were treated with 2.50 mg/kg BW of afoxolaner alone (NexGard; Mérial). For both groups, the tablets were administered directly into the mouth 10 min after eating. Skin scrapings were repeated on days 7, 14, 21, 28, and 56 and the presence or absence of live mites was recorded. The qualification of dermatologic lesions and evaluation of pruritus were repeated on these same days.

Data analysis

The data were captured in a database for further analysis. At the first statistical moment, the distribution of the data was determined and did not present a normal distribution. The data were analyzed and the information on the variables of pruritus and lesions during the week were analyzed by Tukey’s studentized range test with an alpha of 0.05.

Results

The comparison of means of the pruritus level was done on days 1, 7, 14, 21, 28, and 56, as shown in Table I. While the pruritus scale was statistically equal at the beginning of the study, by day 7 there was a significant difference between the 2 treatments, showing a greater decrease in the pruritus level with the combined afoxolaner and milbemycin oxime treatment (group 1). On day 14 and 21, the results were the same and by day 28 the pruritus level had decreased to zero, which was a significant difference from afoxolaner (group 2). On day 56 post-treatment, however, both groups reached 0 on the pruritus scale.

The score of the lesions showed a significant difference from day 1, with a higher value in the dogs given afoxolaner and milbemycin oxime (group 1) on day 7 (Table II). The afoxolaner and milbemycin oxime treatment subsequently presented a notable difference and a greater decrease in the lesions despite the fact that the mean was higher at the beginning of the treatment in dogs treated with afoxolaner alone (group 2). Subsequently, on days 14, 21, and 28, there was also a significant difference between treatments, with a lower score in dogs given afoxolaner and milbemycin oxime (group 1). However, on day 56, which was the last day of testing, the lesion score of both groups had decreased to 0.
Discussion

According to the results of the present study, oral administration of 2.50 to 5.36 mg/kg BW of afoxolaner combined with 0.50 to 1.07 mg/kg BW of milbemycin oxime (NexGard Spectra) significantly reduces the severity of the lesions and reduces the pruritus level to 0 in dogs naturally infested with *S. scabiei* by 28 d. The variability of results in the 142 dogs evaluated in this study demonstrates that sarcoptic mange has no predilection for breed, sex, or age (18,25).

The clinical resolution of pruritus and skin lesions associated with a decrease in the number of mites has previously been reported for products such as selamectin (26), imidacloprid/moxidectin (27,28), fipronil (25), amitraz/fipronil/S-methoprene (29), and topical fluralaner (5). Ivermectin is the most used treatment due to its convenience, low cost, and relative safety in dogs, except in some breeds (30), although cases have been reported that are refractory to treatment (25).

In the present study, the intensity of pruritus decreased significantly over the course of 2 weeks, indicating that afoxolaner plus milbemycin oxime has rapid acaricidal activity. In a previous study, afoxolner demonstrated a reduction in pruritus to 0% associated with a total eradication of mites at 56 d (20). In the present study, although the pruritus level decreased, it continued until day 28 in the dogs given afoxolner alone (group 2). It is therefore possible that the dead mites remaining on the skin continue to cause local irritation for more than 28 d. Fluralaner has been used in similar studies and a decrease of 98% in pruritus was observed on day 28 (3). This was similar to what was previously observed on day 60, with 2 monthly administrations of sarolaner (18). The results obtained show that pruritus was reduced by 87.4%, lower than previously reported with other isoxazolines. It is therefore likely that some mites may still be alive after a month, requiring a second dose to achieve full antiparasitic efficacy.

Milbemycin oxime as a single treatment for sarcoptic mange has also shown good results in reducing pruritus after the third weekly dose, with no adverse effects observed in dogs considered potentially sensitive to ivermectin (23). No adverse effects were observed in this study after the administration of the treatment.

The efficacy of afoxolaner plus milbemycin oxime as an acaricide was also accompanied by a decrease in the rate of lesions characteristic of sarcoptic mange. Fluralaner was used in a previous study and a decrease of 98.92% in the score of the lesions was observed on day 28 (3). This is higher than that obtained in the present study, in which the decrease was 96% on day 28. This is probably related to the higher rate of pruritus until day 28, which could perpetuate the damage. In another study with afoxolaner, a decrease of 60% was observed in the crust index on day 28 (20). This is similar to the results of another study with fluralaner in which a decrease in erythematous papules was observed after 28 d and with sarolaner where a decrease of scabs, erythema, papules, and alopecia was observed on day 60 (18).

In the present study, the intensity of pruritus decreased significantly over the course of 2 weeks, indicating that afoxolaner plus milbemycin oxime has rapid acaricidal activity. In a previous study, afoxolner demonstrated a reduction in pruritus to 0% associated with a total eradication of mites at 56 d (20). In the present study, although the pruritus level decreased, it continued until day 28 in the dogs given afoxolner alone (group 2). It is therefore possible that the dead mites remaining on the skin continue to cause local irritation for more than 28 d. Fluralaner has been used in similar studies and a decrease of 98% in pruritus was observed on day 28 (3). This was similar to what was previously observed on day 60, with 2 monthly administrations of sarolaner (18). The results obtained show that pruritus was reduced by 87.4%, lower than previously reported with other isoxazolines. It is therefore likely that some mites may still be alive after a month, requiring a second dose to achieve full antiparasitic efficacy.

Milbemycin oxime as a single treatment for sarcoptic mange has also shown good results in reducing pruritus after the third weekly dose, with no adverse effects observed in dogs considered potentially sensitive to ivermectin (23). No adverse effects were observed in this study after the administration of the treatment.

The efficacy of afoxolaner plus milbemycin oxime as an acaricide was also accompanied by a decrease in the rate of lesions characteristic of sarcoptic mange. Fluralaner was used in a previous study and a decrease of 98.92% in the score of the lesions was observed on day 28 (3). This is higher than that obtained in the present study, in which the decrease was 96% on day 28. This is probably related to the higher rate of pruritus until day 28, which could perpetuate the damage. In another study with afoxolaner, a decrease of 60% was observed in the crust index on day 28 (20). This is similar to the results of another study with fluralaner in which a decrease in erythematous papules was observed after 28 d and with sarolaner where a decrease of scabs, erythema, papules, and alopecia was observed on day 60 (18).

The rapid ectoparasiticidal effect from the use of afoxolaner alone and afoxolaner plus milbemycin oxime was previously evaluated in a field study of sarcoptic mange in dogs, in which both treatments resulted in substantial improvement of pruritus, papules, and crusts,
and alopecia and was statistically significant within 1 mo after the initial treatment (31).

In the present study, the treatment with afoxolaner combined with milbemycin oxide was associated with a significant reduction in the scores of the lesions between days 1 and 14. Although there were no significant differences between the following days, the score continued to decrease during the rest of the study, although the 28 d between the treatment and the evaluation of the lesions were probably too short to allow complete clinical resolution. It has also been observed that the resolution of the alopecia increases significantly after day 56 (20). However, the results of the present study are consistent with those obtained by Hampel et al (31), with significant differences on day 28 between the natural infestation of mites (Sarcoptes scabiei) and the infestation of the lesions in dogs. Vet Parasitol Res Commun 2011;35:237–244.

In conclusion, the medication in which nematocide milbemycin oxide is added to afoxolaner in order to extend the ectoparasiticidal spectrum of afoxolaner demonstrates a slightly more rapid clinical resolution of clinical signs in spite of the fact that the milbemycin oxide dose is too low. Both afoxolaner alone and the combination of afoxolaner with milbemycin oxide in an oral chewable form are valuable tools for the treatment of scabies since both show high efficacy against canine sarcoptic mange after a monthly dose.

### References


