

Efficacy of a novel formulation of metaflumizone plus amitraz for the treatment of demodectic mange in dogs

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Abstract

A novel spot-on formulation containing metaflumizone plus amitraz (ProMeris[®]/ProMeris Duo[®] for Dogs, Fort Dodge Animal Health, Overland Park, KS) was evaluated for efficacy against demodectic mange mites in naturally infested dogs. Sixteen dogs were allocated to two equal groups and individually housed. Eight of the dogs were treated topically with metaflumizone plus amitraz at the proposed minimum dose rate (20 mg/kg of each of metaflumizone and amitraz, 0.133 ml/kg) on Days 0, 28, and 56. The other eight were treated with metaflumizone plus amitraz at the proposed minimum dose rate on Days 0, 14, 28, 42, 56, and 70. Mite numbers were estimated from skin scrapings taken on Days –3 to –1, 28, 56, and 84. Clinical signs of mange and the extent of demodectic lesions on each dog were evaluated when skin scrapings were conducted. Efficacy of the treatment was based on a reduction in mite numbers and an assessment of the clinical signs associated with canine demodectic mange. Treatment at monthly or two-weekly intervals for 3 months resulted in a rapid reduction in mite numbers (>94 and >99% for the monthly and two-weekly treatments, respectively) and an improvement in clinical signs. Success rates, based on zero mite counts in skin scrapings at Day 84 were 42.9 and 62.5% of dogs for the monthly and two-weekly regimens, respectively.

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1. Introduction

Demodectic mange is an inflammatory parasitic skin disease characterized by a marked increase of *Demodex* spp. mites within the pilosebaceous glands (Paradis, 1999). Small numbers of these mites constitute a normal component of the dog's skin fauna. Three *Demodex* species are implicated in demodectic mange (Shipstone, 2000). *Demodex* spp. mites infest the hair follicles and are usually transferred from the bitch to pups during nursing in the first few days after birth. With the

exception of this initial transfer the disease is not considered to be contagious (Mueller, 2004). Demodectic mange is classified as localized or generalized relative to the extent of the lesions. Localized demodectic mange usually occurs in young dogs (<2 years old), and consists of discrete patches of alopecia, erythema, and comedones, and generally resolves spontaneously (Paradis, 1999). Generalized demodectic mange may develop from the localized condition or occur in older animals in which it is often associated with severe stress or malnutrition resulting in impaired immunity. Generalized demodectic mange, characterized by five or more areas of localized disease, or an entire body region, and pododemodecticosis involving two or more feet, can be categorized as being either of

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juvenile or adult onset. If the disease has persisted for at least 6 months it is considered to be chronic generalized demodectic mange (Paradis and Page, 1998; Shipstone, 2000). Disease with a juvenile onset occurs in animals up to 18 months of age, and that with an adult onset occurs in dogs that are generally older than 4 years of age with no previous history of disease (Shipstone, 2000). The generalized manifestation of the disease is associated with diffuse lesions and with hair loss, and is often aggravated by secondary bacterial infections.

The diagnosis of mange is typically based on clinical signs and is confirmed by the presence of mites in skin scrapings. Treatment is based on chemical control of the mites and supportive therapy for associated conditions (Carter, 2001). Chronic generalized demodectic mange is a frustrating and difficult skin disease to treat (Miller et al., 1993; Medleau and Ristic, 1994). The ailment is unlikely to resolve without treatment (Paradis and Page, 1998). Because the life cycle of the mite extends over a period of 18–24 days (Soulsby, 1982) and in view of the reported difficulties experienced in treating generalized demodectic mange, multiple treatments are advised. Currently available therapeutic options entail daily, weekly, bi-weekly or monthly treatments for periods of 3 months or more (Medleau and Willemse, 1995; Miller et al., 1995; Paradis, 1999; Wagner and Wendleberger, 2000; Heine et al., 2005). Administration of some of the compounds can be labor-intensive and may thus be associated with low owner compliance (Paradis, 1999).

Amitraz dips are the most common treatment with protocols ranging from whole body immersions at various concentrations at intervals of 1–2 weeks (Kwochka et al., 1985; Mueller, 2004) to daily half-body dipping (Medleau and Willemse, 1995). Macrocyclic lactones, orally or by subcutaneous injection, have also been used with some success when administered daily for extended periods at high dose levels (0.2–1.0 mg/kg) (Wagner and Wendleberger, 2000; Mueller, 2004). A moxidectin/imidacloprid spot-on formulation administered at monthly intervals has been shown to be effective against demodectic mange (Heine et al., 2005). Most therapies are, however, relatively laborious, time-consuming, and are associated with potential adverse side effects and may in any event not resolve the infestation (Shaw and Foster, 2000; Mueller, 2004).

ProMeris[®]/ProMeris[®] for Dogs (Fort Dodge Animal Health, Overland Park, KS) is a new product that combines the novel insecticide metaflumizone with the acaricide amitraz in a spot-on formulation, which provides excellent control of fleas and ticks on dogs for up to 1 month (Rugg et al., *this volume*). The safety of this novel formulation has been confirmed following multiple

exaggerated doses administered at two-weekly intervals (Heaney and Lindahl, *this volume*). We report here on an exploratory study aimed at determining the efficacy of this formulation against demodectic mange in dogs when applied at monthly or two-weekly intervals.

2. Materials and methods

The study was carried out at ClinVet International, Bloemfontein, South Africa, and was conducted according to Good Clinical Practice as outlined in VICH GL9, Final Guidance, June 2000, and in accordance with local animal welfare guidelines accepted.

2.1. Animals

Six male and 10 female dogs older than 1 year, purchased from various owners, were used in the study. These animals presented signs of generalized demodectic mange (more than five spots of alopecia, comedones, scales and crusts, pododemodectic mange involving two or more feet, or the entire body was affected). Skin scrapings taken from all the dogs were positive for *Demodex* spp. mites prior to treatment. Each dog was individually identified using neck-bands with numbered tags or by electronic transponders with unique alphanumeric codes. The dogs were of various breeds, mainly mongrels and with the exception of the clinical signs associated with demodectic mange were otherwise healthy on veterinary assessment on Day –9. The animals weighed between 4.9 and 14.9 kg on Day –1. The dogs were acclimated to the study conditions for at least 7 days prior to the initial treatment on Day 0.

The animals were housed individually in kennels that conformed to accepted animal welfare guidelines. Each pen was approximately 3.7 m × 1.7 m with concrete flooring; the indoor sleeping area had under floor heating and the outdoor run area was covered to prevent exposure to rain. No contact between dogs was possible. All dogs were treated for bacterial pyoderma with an appropriate antibiotic, vaccinated and dewormed during the pre-conditioning period. They were observed for general healthiness at least once daily for the duration of the study.

The dogs were fed an appropriate maintenance ration of a commercial dry canine feed throughout the study. Water was available *ad libitum*.

2.2. Experimental design

The investigation was conducted with two groups consisting of eight animals per group. In deference to

animal welfare considerations there was no negative control group.

2.3. Ranking and allocation

Animals were ranked by their Day –1 body weights and randomly allocated to the two treatment groups.

2.4. Treatment

The animals were treated with a commercial formulation containing 150 mg metaflumizone and 150 mg amitraz/ml. Doses were calculated using pre-treatment body weights and were applied to the skin as a single spot between the shoulder blades. The animals in Group 1 were treated at the proposed minimum dose rate of 20 mg/kg of each of metaflumizone and amitraz (0.133 ml/kg) on Days 0, 28, and 56. The dogs in Group 2 were treated at the proposed minimum dose rate on Days 0, 14, 28, 42, 56, and 70.

2.5. Assessments

2.5.1. Mite counts

To assess *Demodex* mite infestations, deep skin scrapings (~4 cm²) were taken on Days –3 to –1, 28, 56, and 84 from five sites on each animal. The initial skin scraping sites were recorded and these sites and/or new lesions were scraped at each subsequent examination. Skin scrapings were made with a blade to the extent that capillary oozing occurred. Each scraping was transferred to a marked (animal i.d., group and body region) microscope slide containing mineral oil and was examined under a stereomicroscope for the presence of live or dead *Demodex* spp. mites and mite eggs. The numbers of immature and adult mites and eggs that were counted in each scraping were recorded separately. The presence of other mite species was recorded but these were not counted. Protective gloves and clothing were changed before handling dogs from different groups.

2.5.2. Clinical signs

The clinical signs and the extent of demodectic lesions on each dog were assessed on the days when scrapings were made. The following parameters were assessed for each dog and sketched on silhouette left and right hand side diagrams: body areas covered with comedones; body areas covered by casts, scales and crusts; body areas with hair loss; body areas with erythema. The animals were also comprehensively photographed at various times during the study.

2.6. Data analysis

Efficacy based on a reduction in mite numbers on dogs in each treatment group relative to pre-treatment numbers, and derived from geometric means (gm), was calculated as follows:

$$\% \text{ Efficacy} = \frac{(\text{gm pre-treatment} - \text{gm post-treatment})}{\text{gm pre-treatment}} \times 100$$

Success rate was defined as the percentage of dogs in each group that were negative for live mites and eggs.

The incidence of the clinical signs of demodectic mange was calculated from the percentage of dogs positive for each sign.

A semi-quantitative assessment of hair regrowth was made. The skin surface of the dogs on which hair regrowth occurred, compared to pre-treatment observations, was scored as 1 if <50% hair regrowth occurred, 2 if 50–90% hair regrowth occurred, and 3 if >90% hair regrowth took place.

3. Results

3.1. Efficacy against demodectic mange

All the dogs were positive for live mites prior to the first treatment. Post-treatment mite and egg counts, and clinical evaluations indicated that treatment regimens of 14 or 28 days with metaflumizone plus amitraz resulted in rapid control of demodectic mange (Tables 1 and 2). Mite counts were reduced from pre-treatment levels by 97.3, 94.2, and 98.6% following the first, second, and third treatments, respectively, in the 28-day treatment regimen. In the 14-day treatment regimen, mite count reductions were >99% of pre-treatment levels at all three evaluations. Success rates (proportion of dogs negative for mites in skin scrapings) at the end of the study were 42.9 and 62.5% for the 28- and 14-day regimens, respectively (Table 1).

3.2. Clinical signs

Clinical signs of demodectic mange and alopecia were also markedly reduced following both treatment regimens (Table 2). The overall appearance of four animals (two mite-free and two mite-positive at the end of the study) before and after treatment in each treatment group is shown in Figs. 1 and 2.

Table 1

The numbers of *Demodex* spp. mites collected from dogs treated for 3 months with metaflumizone plus amitraz spot-on at 28- or 14-day intervals

Evaluation day	Group 1—three treatments at 28-day intervals				Group 2—six treatments at 14-day intervals			
	–3 to –1	28	56	84	–3 to –1	28	56	84
Number of dogs	8	8	7	7	8	8	8	8
Demodex mites								
Mean count	805.2	21.5	46.4	11.3	1284.1	8.6	0.5	5.8
% Reduction	–	97.3	94.2	98.6	–	99.3	>99.9	99.6
Mean egg count	19.4	1.3	0.0	0.0	85.3	0.8	0.0	0.0
% Success rate ^a	0.0	12.5	14.3	42.9	0.0	50.0	87.5	62.5

^a Percent of dogs negative for mites in skin scrapings.

3.3. Health observations

Three dogs (two in Group 1 and one in Group 2) appeared listless on Day 27. Babesiosis was suspected and all three dogs were medicated. Two of the dogs recovered but the third did not recover despite ongoing treatment and was found dead on Day 43. Post mortem examination confirmed the initial diagnosis of babesiosis. Other events were mostly related to gastrointestinal disorders, were mild and did not persist. None of these adverse events were considered to be related to treatment with metaflumizone plus amitraz.

4. Discussion

Demodectic mange, and especially its generalized form, is a common disease that is difficult to treat. Approved topical treatment (and off-label treatment regimens) with amitraz dips are labor-intensive, require repeated application over an extended period of time and are often associated with low levels of compliance and with a number of side effects (Paradis, 1999; Wagner and Wendleberger, 2000). Higher concentrations and/or frequencies of application may result in

greater efficacy (Mueller, 2004), but this increases time and labor inputs and may be associated with a higher incidence of side effects. In a review of the results of treatment against demodectic mange (Mueller, 2004) reported that of 693 cases of juvenile- and adult-onset generalized demodecosis, 65% were in remission after long-term amitraz rinse therapy, 9% were maintained in remission with ongoing treatment, and 25% exhibited no response, or relapsed, or therapy was stopped because of adverse effects. A lower success rate was obtained (32% remission of 72 cases) in cases of adult-onset demodecosis. Similar remission rates have been reported for long-term, high-dose, daily therapy with ivermectin or milbemycin oxime (Miller et al., 1995; Mueller, 2004) and moxidectin (Wagner and Wendleberger, 2000). However, treatment regimens with these macrocyclic lactones are expensive, intensive (daily treatment), lengthy (treatment generally in excess of 3 months), and these high doses may be associated with adverse events.

Treatment with a spot-on formulation of metaflumizone plus amitraz for 3 months at two-weekly or monthly intervals at the minimum proposed dose rate resulted in a rapid reduction in mite

Table 2

Evaluation of the clinical signs associated with demodectic mange and hair regrowth in dogs treated for 3 months with a metaflumizone plus amitraz spot-on at 28- or 14-day intervals

Evaluation day	Group 1—three treatments at 28-day intervals				Group 2—six treatments at 14-day intervals			
	–3 to –1	28	56	84	–3 to –1	28	56	84
Number of dogs	8	8	7	7	8	8	8	8
Frequency of clinical signs								
% Comedones	0.0	0.0	0.0	0.0	12.5	0.0	0.0	0.0
% Casts, scales, crusts	75.0	25.0	14.3	14.3	100	50.0	12.5	12.5
% Erythema	25.0	12.5	0.0	0.0	50.0	25.0	0.0	0.0
Frequency of hair regrowth (%)								
Score 1 = <50%	100	50.0	14.3	0.0	100	87.5	0.0	0.0
Score 2 = 50–90%	0.0	50.0	14.3	28.6	0.0	12.5	75.0	12.5
Score 3 = >90%	0.0	0.0	71.4	71.4	0.0	0.0	25.0	87.5



Fig. 1. Photographs of dogs naturally infested with *Demodex* mites pretreatment (Day –1) and after three treatments with a metaflumizone plus amitraz spot-on at monthly intervals (Day 84).

numbers and a marked improvement in clinical signs in all dogs. Although a significant portion of Group 1 (42.9%) and Group 2 (62.5%) dogs had no mites in their skin scrapings after treatment they cannot be considered as cured. Animals are considered cured only if skin scrapings remain negative for 12 months after the cessation of treatment (Paradis and Page,

1998; Shipstone, 2000) and this was not ascertained in this study. The results of this study nevertheless indicate that the metaflumizone plus amitraz formulation is an efficacious acaricide against *Demodex* spp. mites.

The safety of the metaflumizone plus amitraz combination has been confirmed at doses up to five



Fig. 2. Photographs of dogs naturally infested with *Demodex* mites pretreatment (Day –1) and after six treatments with a metaflumizone plus amitraz spot-on at 14-day intervals (Day 84).

times the proposed dose rates when applied repeatedly at 14-day intervals (Heaney and Lindahl, *this volume*). There were no apparent adverse reactions to treatment in the current study. This confirms that the product would be a safe treatment even when used at treatment intervals of 14 days in dogs suffering from demodectic mange.

5. Conclusions

This study showed that treatment with metaflumizone plus amitraz at the proposed minimum commercial dose rate applied at 14-day or monthly intervals rapidly reduced *Demodex* mite infestations on dogs and resulted in a marked clinical improvement in the symptoms

associated with demodectic mange. The metaflumizone plus amitraz formulation is an easy to use, safe and efficacious acaricide that can potentially be used in conjunction with other supportive therapies to treat generalized canine demodecosis.

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