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Dose determination of a novel formulation of metaflumizone plus amitraz for control of cat fleas (*Ctenocephalides felis felis*) and brown dog ticks (*Rhipicephalus sanguineus*) on dogs

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Abstract

A novel spot-on formulation containing metaflumizone and amitraz (ProMeris®/ProMeris Duo® for Dogs, Fort Dodge Animal Health, Overland Park, KS) was evaluated in a laboratory study to determine the appropriate dose for efficacy against fleas and ticks on dogs for 1 month. Thirty-six Beagles were randomly allocated to six equal groups and individually housed. One group remained nontreated. Another was treated with a placebo formulation (solvents with no active ingredients). Three groups of dogs were treated topically with the metaflumizone plus amitraz formulation (150 mg of each of metaflumizone and amitraz/ml), at volumes providing doses of 10, 20 and 40 mg each active/kg. The final group was treated with a commercial spot-on providing 6.7 mg fipronil/kg. All treatments were applied to the skin at a single spot between the scapulae on Day 0. Dogs were infested with 50 adult brown dog ticks (*Rhipicephalus sanguineus*) on each of Days −2, 5, 12, 19, 26, 33 and 40, and with 100 cat fleas (*Ctenocephalides felis felis*) on Days −1, 6, 13, 20, 27, 34 and 41. Dogs were examined and parasites ''finger counted'' on Day 1 to estimate knock down efficacy, and all animals were comb counted to determine the numbers of viable fleas and ticks on Days 7, 14, 21, 28, 35 and 42. There were no significant differences in parasite counts between the nontreated control and the placebo-treated control groups for either fleas or ticks ($P > 0.05$) except for very slight reductions on Day 7 for fleas and Day 14 for ticks, demonstrating that the formulation excipients had no activity. The qualitative finger counts on Day 1 indicated that all of the insecticidal treatments resulted in a noticeable reduction in flea and tick numbers within 1 day of treatment. All of the metaflumizone and amitraz treatments and fipronil resulted in significantly lower flea and tick numbers relative to nontreated controls on all posttreatment count days ($P < 0.05$). For the metaflumizone plus amitraz treatments, mean flea and tick counts for the 10 mg/kg dose were significantly higher than those for the 20 mg/kg dose ($P < 0.05$) from Day 21 on. There was no significant advantage provided by the 40 mg/kg dose over the 20 mg dose throughout the entire study ($P > 0.05$). The two higher metaflumizone plus amitraz doses provided >95% control of fleas and >90% control of ticks for at least 35 days after treatment, and this level of control was similar to that of the commercial fipronil product. The 20 mg/kg dose was selected as the minimum commercial dose rate to provide effective flea and tick control for at least 1 month following a single treatment.

Keywords: ProMeris®; ProMeris Duo®; *Ctenocephalides felis felis*; *Rhipicephalus sanguineus*; Metaflumizone; Amitraz; Flea; Tick; Dog

1. Introduction

Permanent or semi-permanent ectoparasites occurring on dogs are mainly fleas, ticks and mites. Of these, the cat flea (*Ctenocephalides felis felis*) is the most

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widespread, being endemic worldwide and considered the most important ectoparasite of dogs and cats (Rust and Dryden, 1997). Adult fleas are blood feeders, penetrating the skin with their sucking mouthparts and injecting salivary antigens as they feed. They are recognized as a major cause of allergic skin disease in dogs and are capable, when present in sufficient numbers, of causing anaemia (Krämer and Menke, 2001). They are intermediate hosts for the dog tapeworm, *Dipylidium caninum*, and can transmit a number of pathogens including *Bartonella henselae*, which causes cat scratch fever (Krämer and Menke, 2001).

Infestations of ticks on dogs can be anything from an occasional nuisance to a continuous infestation, and range from having virtually no adverse effects on health to causing life-threatening disease. All stages of ticks feed by first slashing the host's skin with their chelicerae to gain entry, then piercing a blood vessel and inserting their mouthparts into, or close to, the blood vessel. Large amounts of blood are taken up by the tick, excess water is removed and returned to the host in the form of saliva, which contains a number of pharmacologically active substances, including anticoagulants and immunomodulators, the exact components varying between species. Some tick species excrete toxic substances within their saliva and tick-borne diseases are normally passed to their next host in saliva (Needham and Teel, 1991). Where tick populations are large, numbers may be high enough to cause anaemia. Ticks are responsible for the transmission of a number of diseases, some are dog-specific, some are zoonotic and some cause serious, even life-threatening, diseases (Dryden and Payne, 2004). *Babesia canis* and *Ehrlichia canis* are both dog-specific infections, the former primarily transmitted by *Dermacentor* spp. and the latter by the brown dog tick, *Rhipicephalus sanguineus*. Zoonotic infections include Lyme disease caused by *Borrelia burgdorferi*, which is transmitted by *Ixodes* spp., and Rocky Mountain Spotted Fever, caused by *Rickettsia rickettsii*, which is transmitted primarily by ticks in the genera *Amblyomma*, *Dermacentor* and *Ixodes* (Dryden and Payne, 2004).

Control of fleas and ticks is primarily based on chemical means and recently, convenient topical treatments have become the standard accepted method (Dryden and Payne, 2004; Rust, 2005). The most widely used products are generally applied as spot-on applications on a monthly schedule and include compounds with efficacy against both fleas and ticks, as well as specific insecticides or acaricides. A number of chemical classes are used for flea and/or tick control and include: the phenyl pyrazole, fipronil; the neonicotinic, imidacloprid; the synthetic pyrethroids, permethrin and phenothrin; and the avermectin, selamectin (Rust, 2005). Of these imidacloprid is a specific insecticide with little efficacy against ticks (Krämer and Menke, 2001) while the others are effective against both fleas and ticks. These all have direct insecticidal/acaricidal activity and control the parasites on the animal. In addition, there are products such as insect growth regulators that may be fed (lufenuron) or applied (s-methoprene) to the pet but control fleas by disrupting the off-host life stages (eggs and larvae), and others (e.g. pyriproxyfen) that may be used for environmental applications. Despite the variety of available products and different application methods, both fleas and ticks remain an ongoing problem for many pet owners. Also, the susceptibility of populations may decrease with prolonged exposure to individual products. Fleas have potentially developed resistance to a number of compounds and pest management strategies to reduce the development of resistance are needed (Bossard et al., 1998; Ross et al., 1998; Rust, 2005).

Metaflumizone is a novel insecticide in the semicarbazone class of chemistry with no known cross-resistance to other chemistries (Salgado and Hayashi, this volume). This insecticide was combined with the formamidine acaricide amitraz in a novel spot-on formulation to develop a product for flea and tick control on dogs. This study was conducted to determine the appropriate dose rates of a formulation of metaflumizone and amitraz (ProMeris®/ProMeris Duo® for Dogs, Fort Dodge Animal Health, Overland Park, KS) applied as a single spot application to dogs to provide at least 1 month of control of fleas and ticks.

2. Materials and methods

The study was conducted at Nu-Era Farms, OK. The study was conducted according to Good Laboratory Practices as outlined in US EPA 40CFR160, and followed the basic methodology of US EPA Guideline 810.3300.

2.1. Animals

Eighteen male and 18 female adult Beagle dogs, 3–7 years of age from the Nu-Era Farms colony were used in the study. Each dog was individually identified by numbered or lettered ear tattoos. The dogs had not been treated with an ectoparasiticide for at least 60 days and were in good health when enrolled in the study and at treatment. The animals weighed from 9.3 to 16.6 kg on