

COMPARISON OF EFFICACY, SIDE EFFECTS, AND COST OF ISOXASOLINES
AND IVERMECTIN AGAINST GENERALIZED CANINE DEMODICOSIS

By

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Abstract

Demodex canis mites are found in the normal skin microbiota of most dogs, but can result in canine demodicosis if the number of mites dramatically increases due to underlying disease, immunosuppression, genetic defect, stress, or breed association. Treating generalized Demodectic mange often requires high owner compliance over a potentially long period of time, especially when using ivermectin. Recent studies have revealed that a class of insecticides known as isoxasolines provide a better alternative for treatment of generalized demodicosis, specifically afoxolaner (NexGard®), fluralaner (Bravecto™), and sarolaner (Simparica™). This review compares the efficacy, side effects, and cost of isoxasolines to ivermectin in efforts to aid owners and veterinarians in choosing an effective, yet safe and low-cost treatment option. Although additional studies are needed, fluralaner appears to be highly efficacious and the safest and cheapest treatment option for generalized canine demodicosis, while ivermectin appeared to be the least preferred treatment option presently, a major factor being toxicity.

Introduction

Demodex canis mites are found in the normal skin microbiota of most dogs, residing in the sebaceous glands connected to hair follicles¹. When the number of the mites dramatically increase, an inflammatory parasitic disease known as canine demodicosis results¹. The disease can be classified into two groups: localized and generalized. Localized demodicosis usually occurs in younger dogs (<2 years) and presents with small areas of nonpuritic alopecia and erythema². The disease typically regresses spontaneously with no treatment needed. Conversely, generalized demodicosis can be much more severe and almost always needs treatment². While differentiating between localized and generalized can be difficult, generalized demodicosis is usually characterized as more than five affected lesions or an entire area of the body². Generalized *Demodex* can occur in older dogs and may arise from localized lesions, an underlying disease, immunosuppression, genetic defect, stress, or be breed associated³. Demodicosis can be diagnosed by observed clinical signs and identifying mites on a deep skin scraping.

In the past, treating generalized Demodectic mange has been challenging and often required high owner compliance over a potentially long period of time⁴⁻⁶. Forms of treatment include topical rinses and dips, subcutaneous injections, and oral medication. Dips and injections can be inconvenient for owners, potentially toxic, and costly. Recent studies have revealed that a class of insecticides known as isoxasolines provide a better alternative for treatment of generalized demodicosis, specifically afoxolaner (NexGard®), fluralaner (Bravecto™), and sarolaner (Simparica™). These drugs are relatively low cost, much easier for dosing and administration, and show little adverse side effects⁷⁻¹⁰. The purpose of this review is to compare the efficacy, side effects, and cost of isoxasolines to ivermectin. While other treatment options exist, the treatments discussed here are those which reflect the owner's best interest of time, cost, and safety.

Efficacy

Despite their surprisingly low frequency of dosing required, the efficacies of isoxasolines are excellent. For both fluralaner and afoxolaner, 8 dogs were diagnosed with generalized demodicosis by deep skin scrapings. In the fluralaner study, each dog was dosed at 25mg/kg only once on day 0⁷. Afoxolaner was dosed at a concentration of 2.5mg/kg on days 0, 14, 28 and 56 (totaling four doses)^{9,10}. Skin scrapings in five locations were performed on each dog at day 0, 28, 56, and 84. Fluralaner had an efficacy rate of 99.8% on day 28, and 100% on day 56 and 84⁷. Afoxolaner had an efficacy rate of 99.2%

by day 28, 99.9% by day 56, and 100% by day 84⁹. Sarolaner was dosed 2mg/kg on days 0, 30, and 60 (totaling three doses). The efficacy rate was 97.8% on day 14, 99.8% by day 29, and 100% by days 44, 59, 74, and 91⁸. Statistically significantly ($P \leq 0.05$) fewer mites were recorded from the dogs in the afoxolaner-, fluralaner-, and sarolaner-treated group compared to the imidacloprid/ moxidectin-treated group⁷⁻⁹.

Many studies have been conducted on the efficacy of oral ivermectin against Demodex over the past decade, and the reported efficacy varies, possibly because of different dosing regimens and levels of severity. In a recent trial, 58 dogs suffering from generalized demodicosis were randomly treated with monthly, biweekly or weekly applications of Advocate®, or with daily oral ivermectin at 500 µg/kg¹¹. Oral ivermectin was significantly more efficacious than was ADV weekly application ($P = 0.003$) and showed 99% efficacy after 4 months¹¹. Another study reported an 85% cure rate in 20 dogs diagnosed with generalized demodicosis dosed orally with 0.6 mg/kg of daily ivermectin¹². It should be noted that ivermectin was administered on an “as needed” basis; depending on the study, each dog was evaluated every 4 weeks for 4 months or until negative scrapings at all sites resulted on two successive evaluations (parasitological cure)¹¹. Dogs receiving daily ivermectin treatment often relapse, or present with mites less than 1 year after the last dose¹³. One study reported that, on a dosing regimen of 3.5mg/kg daily ivermectin, five of ten dogs relapsed 1-12 months following last administration of treatment¹⁴. Oral ivermectin and amitraz treatment was instituted and one of these five cases that relapsed was in remission for more than 6 months, two dogs were in remission for less than 6 months, and two dogs were still receiving treatment at time of publication¹⁴. Follow up examinations were not conducted in the sarolaner, fluralaner, or afoxolaner studies⁷⁻¹⁰ after the final exams on days 56, 84, and 91, so long term cure rates and number of relapses are unknown for these 3 drugs.

According to the data discussed, fluralaner or sarolaner had the highest efficacy rate of 99.8% mite reduction on Day 28/29, a day that was consistently evaluated between all four studies of isoxasolines^{7,8,9,11}. If based solely on efficacy, fluralaner or sarolaner would be the preferred choice of treatment for generalized canine demodicosis.

Cost

Cost can be a key deciding factor for many owners when choosing a treatment for demodicosis. Cost varies between pharmacies, vet clinics, and other sources, so the price examples and comparisons provided in this article may not be definitive. Vallyvet.com, a popular Vet-VIPPS accredited pet pharmacy, is the source used here to determine prices for each drug. Prices will differ based on the weight of the animal and quantity of drug required, so an average 30lb animal is used as an example here.

Fluralaner only requires one oral dose for full treatment, assuming no relapse. One chewable Bravecto™ fluralaner tablet costs \$36.99 at Valleyvet.com. As for afoxolaner, efficacy can be reached with either three or four treatments orally administered every four weeks. Assuming a three dose-treatment protocol, a 3-pack of NexGard® afoxolaner chewable tablets is priced at \$53.49. Sarolaner efficacy, assuming no relapse, can be reached after three orally administered treatments, each 30 days apart. Simparica™ sarolaner chewable tablets are at Valleyvetmeds.com at \$38.49 for 3 tablets. Ivomec® is undiluted ivermectin formulated for use in cattle originally sold as an injectable, but is administered orally for dogs diagnosed with demodex¹¹. A 50mL bottle of Ivomec® for Cattle and Swine injection, which is enough to dose 150,000 pounds of dog when fully diluted, is \$37.95. Bravecto™ fluralaner tablets are the most cost-effective treatment option, a mere \$.96 cheaper than Ivomec® ivermectin.

Side effects

No adverse side effects have been observed related to treatment in all three isoxasolines studies⁷⁻¹⁰. It should be noted that only one study for fluralaner, one study for sarolaner, and two studies for afoxolaner have analyzed the safety and efficacy against *Demodex manges*. Each study had a sample size of 8, 16, and 12 respectively. More research with larger sample sizes and varying doses should be conducted to determine if adverse side effects arise in animals treated with isoxasolines for demodicosis.

High dose regimens of ivermectin in dogs have been shown to cause neurologic, adverse side effects such as mydriasis, tremors, seizures, ataxia, coma, lethargy, and blindness¹⁵. In the imidacloprid/moxidectin comparison to ivermectin study mentioned previously¹¹, 2 of the 58 dogs experienced severe neurotoxicosis from ivermectin and were withdrawn from the trial. Another clinical trial evidenced 1 of 12 dogs developing ivermectin toxicosis after 5 weeks of treatment¹³. A different study measuring a gradual increase in ivermectin dosage found that only 2 of 222 dogs developed ivermectin toxicity, at two and ten days after beginning treatment, which resolved after ivermectin was stopped¹⁶. To avoid potential toxicosis, a gradual dose increase from 0.05 mg/kg on day 1 to 0.1 mg/kg on day 2, 0.15 mg/kg on day 3, 0.2 mg/kg on day 4 and 0.3 mg/kg on day 5 is recommended for dogs being treated with ivermectin¹⁶. Acute ivermectin toxicity with severe neurological side effects has been observed in certain collie and herding breeds prone to MDR-1 mutation^{17,18}, even at low dosages which are not toxic in dogs lacking the mutation. This gene can be tested for and detected at Washington State University prior to treatment. The mutation results in an abnormal P-glycoprotein transcription which allows the insecticide to penetrate the central nervous system and cause neurotoxicity¹⁷. However, evidence shows that dogs who do not possess the mutation are still susceptible to ivermectin toxicity, so lack of MDR-1 mutation does not prevent toxicosis¹⁹. Prolonged daily ivermectin treatment may result in chronic toxicity from cumulative therapy²⁰. Side effects usually resolve under supportive care, shortly after treatment is stopped.

Conclusions

While additional studies are needed, fluralaner appears to be highly efficacious and the safest and cheapest treatment option for generalized canine demodicosis. Bravecto® fluralaner chewable tablets are lowest in price and share a high efficacy rate with Simparica™ sarolaner tablets. Ivermectin appeared to be the least preferred treatment option presently, when analyzing price, efficacy, and especially toxicity risk^{11-13,17,18}.

Furthermore, treating with fluralaner only requires one dose, compared to bi-monthly/monthly dosing of afoxolaner and sarolaner, and daily dosing with ivermectin. The price, efficacy, lack of adverse side effects, and one-time dosing of fluralaner would make this treatment convenient and appealing for owners, especially if there is no evidence of long term relapse.

References

1. Scott, D.W., Miller, W.H., Griffin, C.E. *Muller and Kirk's Small Animal Dermatology*, 5th ed. W.B. Saunders, Philadelphia 1995; p. 417–32.
2. Guaguère, E., Beugnet, F. A practical guide to canine dermatology. Kaliaxis: Paris. 2008; p. 179–226.
3. Singh K.S., Dimri, U. 2014. The immuno-pathological conversions of canine demodicosis. *Vet Parasitol* 2014; 203:1–5.
4. Medleau L., Ristic Z. Treating chronic refractory demodicosis in dogs. *Veterinary Medicine* 1994; 89:775–7.
5. Burrows, A. K. Generalised demodicosis in the dog: the unresponsive or recurrent case. *Australian Veterinary Journal* 2000; 78(4), 244-246.
6. Mueller, R.S. Treatment protocols for demodicosis: an evidence-based review. *Veterinary Dermatology* 2004; 15:75–89.
7. Fourie, J. J., Liebenberg, J. E., Horak, I. G., Taenzler, J., Heckerroth, A. R., & Frénais, R. Efficacy of orally administered fluralaner (Bravecto™) or topically applied imidacloprid/moxidectin (Advocate®) against generalized demodicosis in dogs. *Parasites & vectors* 2015; 8(1), 187.
8. Six, R. H., Becskei, C., Mazaleski, M. M., Fourie, J. J., Mahabir, S. P., Myers, M. R., & Sloomans, N. Efficacy of sarolaner, a novel oral isoxazoline, against two common mite infestations in dogs: *Demodex* spp. and *Otodectes cynotis*. *Veterinary Parasitology* 2016; 222, 62-66.
9. Beugnet, F., Halos, L., Larsen, D., & de Vos, C. Efficacy of oral afoxolaner for the treatment of canine generalised demodicosis. *Parasite* 2016; 23.
10. Chávez, F. Case report of afoxolaner treatment for canine demodicosis in four dogs naturally infected with *Demodex canis*. *J Appl Res Vet Med* 2016; 14(2), 123-7.
11. Paterson, T. E., Halliwell, R. E., Fields, P. J., Louw, M. L., Ball, G., Louw, J., & Pinckney, R. Canine generalized demodicosis treated with varying doses of a 2.5% moxidectin+ 10% imidacloprid spot-on and oral ivermectin: Parasitocidal effects and long-term treatment outcomes. *Veterinary Parasitology* 2014; 205(3), 687-696.
12. Medleau, L., Ristic, Z., Paradis, M., & McElveen, D. Efficacy of daily ivermectin therapy for generalized demodicosis in dogs: a comparison of two dosages. In *Proceedings annual Meeting of AAVD/ACVD, Santa Fe* 1995; (Vol. 50).
13. Medleau, L., Ristic, Z., and McElveen, D.R. Daily ivermectin for treatment of generalized demodicosis in dogs. *Veterinary Dermatology* 1996; 7(4), 209-212.
14. Fondati, A. Efficacy of daily oral ivermectin in the treatment of 10 cases of generalized demodicosis in adult dogs. *Veterinary Dermatology* 1996; 7(2), 99-104.
15. Mueller, R. S., Bensignor, E., Ferrer, L., Holm, B., Lemarie, S., Paradis, M., & Shipstone, M. A. Treatment of demodicosis in dogs: 2011 clinical practice guidelines. *Veterinary dermatology* 2012; 23(2), 86-e21.

16. Mueller R.S., Bettenay S.V. A proposed new therapeutic protocol for the treatment of canine mange with ivermectin. *Journal of the American Animal Hospital Association* 1995; **35**: 77–80.
17. Mealey K.L., Bentjen S.A., Gay J.M. *et al.* Ivermectin sensitivity in collies is associated with a deletion mutation of the *mdr1* gene. *Pharmacogenetics* 2011; **11**: 727–733.
18. Roulet A, Puel O, Gesta S *et al.* MDR1-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. *European Journal of Pharmacology* 2003; **460**: 85–91.
19. Bissonnette, S., Paradis, M., Daneau, I. *et al.* The ABCB1-1 Δ mutation is not responsible for subchronic neurotoxicity seen in dogs of non-collie breeds following macrocyclic lactone treatment for generalized demodicosis. *Veterinary Dermatology* 2009; 20: 60–66.
20. Lo, P.-K.A., Fink, D.W., Williams, J.B. *et al.* Pharmacokinetic studies of ivermectin: effects of formulation. *Veterinary Research Communications* 1985; **9**: 251–68.