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Double-blinded Crossover Study with Marine Oil Supplementation Containing High-dose Eicosapentaenoic Acid for the Treatment of Canine Pruritic Skin Disease*

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Abstract—The objective of this double-blinded crossover study was to examine the effects of marine oil supplementation with high-dose eicosapentaenoic acid (EPA) on canine pruritic skin disease. Sixteen dogs that completed this study had clinical signs related to idiopathic pruritus, confirmed atopy and/or flea allergy. Each dog was randomly placed on one omega-3 fatty acid capsule (MVP: Meridian Veterinary Products, St. Augustine, FL, U.S.A.) which contained 1 ml of marine oil (180 mg EPA and 120 mg DHA) or one capsule containing 1 ml of corn oil (570 mg linoleic acid and 50 mg gamma linolenic acid) per 4.55 kg of body weight q 24 h for 6 weeks. After a 3-week washout period in which no supplement was given, each subject was crossed over to the other supplement for an additional 6 weeks. Dogs receiving marine oil showed a significant improvement in pruritus ($P < 0.001$), self-trauma ($P < 0.05$) and coat character ($P < 0.01$) over time. When compared to the corn oil control over time, marine oil supplementation significantly improved pruritus ($P < 0.02$), alopecia ($P < 0.05$) and coat character ($P < 0.001$). This study demonstrates the effectiveness of high doses of marine oil as an alternative anti-inflammatory for canine pruritic skin disease.

Key Words: Canine; Omega-3 fatty acids; Eicosapentaenoic acid; Pruritic dermatitis.

INTRODUCTION

Currently, numerous fatty acid supplements are marketed to veterinarians as safe, effective alternatives to systemic glucocorticoids in the treatment of canine pruritic skin disease. The majority of these supplements contain a mixture of polyunsaturated fatty acids (PUFA) including *n*-3 PUFA, such as eicosapentaenoic acid (EPA) and docosahexanenoic acid (DHA). In theory, the addition of EPA and DHA to the diet causes the displacement of arachidonic acid (AA) with EPA or DHA in cell membranes and a subsequent decrease in production of proinflammatory eicosanoids from AA for the less inflammatory eicosanoids of EPA. This leads to a modification of both platelet and neutrophil responses which in turn decreases clinical evidence of inflammation (1–3). These concepts have been extensively reviewed elsewhere (4–9).

The reported effectiveness of marine oil in the available veterinary fatty acid supplements (Derm Caps: DVM, Miami, FL, U.S.A. and Efa Vet: Efamol, Guildford, U.K.) to control canine pruritus has been varied (8–15). Several studies that were not placebo-controlled reported substantial decreases in pruritus, while other studies demonstrated no statistically significant decreases. However, the standard dosage of EPA in these supplements is considerably less than the doses that have been effective in controlling pruritus in human atopics (16).

The purpose of this study was to examine the effects of high-dose EPA supplementation (MVP: Meridian Veterinary Products, St. Augustine, FL, U.S.A) on canine pruritic skin disease in a double-blinded crossover manner.

MATERIALS AND METHODS

The dogs used for this study were chosen from patients seen by the Dermatology Service at the

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Veterinary Medical Teaching Hospital. Dogs were accepted into the study if they currently had visible signs of pruritic skin disease such as erythema, self-trauma, abnormal coats and alopecia due to confirmed flea allergy and/or confirmed or presumed atopy and their symptoms were not entirely caused by food allergy. Dogs were confirmed flea allergic if they had clinical signs consistent with this condition and were intradermal skin test-positive to flea antigen (17). They were considered confirmed atopics if they had clinical signs consistent with atopy and were intradermal skin test-positive to one or more allergens other than flea (17). They were considered to have idiopathic pruritus if their clinical signs were compatible with atopy, they did not respond to a hypoallergenic diet and had a negative intradermal skin test (18). Food allergic dogs were accepted into the study if a hypoallergenic food trial failed to completely eliminate pruritus and if they were currently being fed an appropriate hypoallergenic diet. Subjects were excluded from the study if they were currently on glucocorticoid or essential fatty acid therapy; they had concurrent demodicosis, dermatophytosis or sarcoptic mange; or they were not being fed a nutritionally complete maintenance diet as their primary diet. If a dog presented with a bacterial pyoderma, this was treated appropriately with antibiotics prior to enrolment in the trial. Once accepted into the study, each subject had to be maintained on its current flea control, topical therapy and appropriate diet throughout the entire course of the project.

Upon entering the study, dogs were physically examined by the primary investigator (D. Logas) to assess erythema, self-trauma (hyperpigmentation, lichenification, excoriations, crust), coat quality (gloss, softness, degree of seborrhea) and alopecia. Each parameter was scored on an increasing scale of 0–10 (0—absent or normal). The severity, chronicity and extent of the lesions were all subjectively assessed on physical examination by the investigator to generate the baseline score for each parameter. Pruritus was assessed for each dog by the primary investigator using a combination of the investigator's and owner's observation of pruritic behaviors such as licking the feet/inguinal area, chewing the feet/trunk, scratching the head/trunk and rubbing the head/trunk. The same 0–10 scale was used to subjectively quantitate pruritus. The score was based mainly on the owner's perceptions of the intensity, frequency and extent of the pruritus. The dogs were then randomly assigned in a double-blinded manner to one of the two treatment groups. The first group received a 1-ml capsule of omega-3 fatty acid (180 mg EPA and 120 mg of docosahexaenoic acid/capsule) per 4.55 kg of body weight orally q 24 h. The second group (control group) received a 1-ml capsule of corn oil (540 mg linoleic acid and 50 mg dihomogamma linolenic acid/capsule per 4.55 kg of body weight orally q 24 h. The treatment dose of EPA was designed to approximate the dose reported to have been effective in the treatment of human patients with atopy and rheumatoid arthritis (16, 19). The initial treatment period of 6 weeks was followed by a 3-week washout period in which no supplement was given. The washout period was designed to allow any effects on the composition of the cellular membrane phospholipids to return to normal (20–22). Each dog was then crossed over to oral administration of the other supplement for an additional 6 weeks.

The dogs were re-evaluated by the primary investigator at 3-week intervals throughout the 15-week project. At each re-evaluation the dogs were examined for the severity, chronicity and extent of their erythema, alopecia and self-trauma and for their coat quality. The physical description for each parameter was compared to the description from the previous visit. Using this comparison a new numerical score was generated by determining the change from the previous visit. Pruritus was re-evaluated at each recheck by asking the owners to quantitate the pruritic activities of their dog and then to determine a percentage of change from baseline and the previous visit. This percentage of change was used to help calculate a new pruritus score. At the completion of the study, the owners were asked to compare the two supplements and determine if either or both supplements had improved or worsened their pets' overall skin condition taking into account pruritus, alopecia, self-trauma and coat quality compared to their pets' condition before either supplement was given. The owners were asked to subjectively quantify these changes as a slight (<25 per cent), mild (25–50 per cent), moderate (50–75 per cent) or marked (>75 per cent) change when compared to their pets' overall condition before supplementation. To help assure owner compliance at each recheck the owners were asked to personally observe their pet consuming the capsules and to return the empty capsule bottles.

STATISTICAL ANALYSIS

Analysis of variance with repeated measures was used to compare the mean score of each parameter for each group taken at each assessment period to each of its other assessment periods and to the mean score of the other group at each assessment period. A difference over time or between groups was considered significant if $P < 0.05$. The computer software utilized for these calculations was SAS (SAS Institute Inco, SAS User's Guide. Edition G: System for Lines Models; Cary, NC 1986).

RESULTS

Nineteen dogs were accepted into the study. Sixteen completed all 15 weeks of the study. One dog

dropped out because of owner noncompliance, another for persistent vomiting and one dog died of unrelated causes during the trial. Eight of the 16 were diagnosed as flea allergic, five were confirmed atopics, two had idiopathic pruritus and one dog's signs were related to both atopy and flea allergy.

When asked to compare the two supplements at the end of the study, 11 of 16 owners determined that their dogs' overall condition (pruritus, coat quality, alopecia and self-trauma) improved on marine oil (2/11 determined their pets were 25–50 per cent improved, 3/11 50–75 per cent and 6/11 > 75 per cent improved); 3 of 16 owners determined their dogs improved on corn oil (2/3 < 25 per cent improved, 1/3 25–50 per cent improved); 2 of 16 determined that their dogs either worsened or remained static on both supplements; and no owner perceived their dogs' overall condition substantially improved on both supplements when compared to their dogs' overall condition before either supplement was given. When compared by diagnosis, 6 of 8 dogs with flea allergy, 3/5 with atopy, 1/2 with idiopathic pruritus and 1/1 with atopy and flea allergy improved on marine oil supplementation.

The means of each parameter for each group were calculated and are listed in Table 1. Over time, none of the parameters were significantly improved by the corn oil, while coat character ($P < 0.01$), pruritus ($P < 0.001$) and self-trauma ($P < 0.05$) were significantly improved by marine oil. When the two supplements were compared to each other over time, the improvement with marine oil was significantly better than corn oil for alopecia ($P < 0.05$), pruritus ($P < 0.02$) and coat character ($P < 0.001$).

CONCLUSIONS

This study indicates that marine oil supplementation at a dose of EPA at least 5-times and a dose of DHA at least 6-times greater than those currently recommended or reported in other canine studies (8–15) can significantly decrease the symptoms associated with canine pruritic skin disease. In this study 56 per cent (9/16) of the dogs on marine oil had an obvious moderate-to-marked improvement in their clinical signs when pruritus, coat quality, alopecia and self-trauma were all taken into account, while only 6 per cent (1/16) had a moderate improvement in overall clinical signs on corn oil. The study does not suggest that this is the optimal dose. It is conceivable that a higher dose may precipitate further improvement or a lower dose may achieve the same results. The optimal EPA dosage is not known for any species. There have been a wide range of dosages used in both human (1–3.2 g of EPA.day^{-1}) and canine (1–8 mg.kg^{-1}.day^{-1}) studies with varied results. The dose in this study was extrapolated from and comparable to a dose (1.8 g EPA daily) which significantly decreased the symptoms of human atopic patients and one (2.7 g EPA daily) that significantly decreased the symptoms of human rheumatoid arthritis patients (16, 19). The dose used in this study was also considered safe since in a previous study 38 mongrel dogs given 1.8 g EPA daily for 7 weeks had no adverse side effects (28).

Corn oil was used as a placebo or control in this study instead of olive oil which has been used previously (15, 16, 19). The ratio of corn oil polyunsaturated to monounsaturated fatty acids is closer to our

TABLE 1. Comparison of the means of EPA and corn oil in the five examined parameters*

	Week 0	Week 3	Week 6
Pruritus†			
Marine oil ($n = 16$)	7.13 ± 2.25	5.81 ± 2.90	4.44 ± 3.56‡ ± 3.56
Corn oil ($n = 16$)	6.44 ± 3.63	6.56 ± 3.37	6.06§ ± 3.61
Erythema			
Marine oil	2.50 ± 2.76	2.19 ± 2.93	1.88 ± 2.39
Corn oil	1.56 ± 2.31	2.31 ± 2.18	2.38 ± 2.22
Self-trauma†			
Marine oil	3.00‖ ± 2.50	2.13 ± 1.96	1.81‖ ± 2.61
Corn oil	2.56 ± 2.00	2.63 ± 1.26	2.44 ± 1.59
Coat character†			
Marine oil	2.88¶ ± 2.63	1.56 ± 2.06	1.25¶** ± 1.80
Corn oil	2.56 ± 2.10	3.19 ± 2.79	2.88** ± 2.50
Alopecia†			
Marine oil	1.81 ± 2.14	1.25 ± 2.08	1.00†† ± 1.79
Corn oil	1.69 ± 2.07	1.94 ± 1.88	2.25†† ± 1.88

*Scale used for all parameters: 0–10 (0—absent or normal).
†Significant difference found between means with similar superscripts.
‡$P < 0.001$.
§$P < 0.02$.
‖,††$P < 0.05$.
¶,**$P < 0.01$.

supplement than is olive oil. Corn oil also contains mainly *n*-6 PUFA with little to no *n*-3 fatty acids. Corn oil and our marine oil supplement change the diets' polyunsaturated to saturated ratio (P/S) similarly; therefore, the difference between the groups would be mainly the difference in *n*-3 to *n*-6 fatty acids not the difference in P/S fatty acids. Corn oil was therefore a reasonable placebo to use in this study.

Several design flaws in our study were evident during data analysis. Since we included no laboratory indices to assess tissue or serum fatty acid levels, it was impossible to confirm owner compliance. We attempted to compensate for this by having the owners return the empty capsule containers at each recheck and by having them demonstrate to the investigator that the pet would consume the capsules.

Another problem is our decision to use a 3-week washout period. At the time of this study's conception, this was considered an appropriate washout period. In earlier veterinary studies, no washout period was used (23). In various human studies the washout period was 4 weeks (19, 24). Unfortunately, new evidence is emerging that 3 weeks may not be long enough for *n*-3 fatty acids incorporated into cell membrane phospholipids to dissipate (25). We had no serum or tissue fatty acid levels to evaluate to determine if the EPA and AA levels had returned to baseline after the 3-week period. To assess the possible effects of residual marine oil on our clinical evaluations we compared the mean values of the following four groups for all five parameters using a permutation test for ordered categorical data. The groups were "dogs started on marine oil at week 0", "dogs started on marine oil at week 9", "dogs started on corn oil at week 0" and "dogs started on corn oil at week 9". There was no significant difference among any of the groups for any of the five parameters ($P > 0.3$; data not included), therefore, at least clinically our 3-week washout period was adequate.

Another problem in performing a clinical trial using subjective data is consistency in the data. To help overcome this we used a crossover design so each dog would act as his own control. We tried to keep our data consistent by giving each parameter a baseline score determined by severity and extent of the lesion and then calculated subsequent scores based on the parameter's change from the previous visit. The subjectivity of the data was best demonstrated when scores of pruritus were compared to those of other parameters. The disparity is most likely due to the fact that the pruritus scores were mainly determined by owners' perceptions of pruritic behaviors while the scores of the other parameters were based solely on the investigator's physical examination. This disparity does not invalidate the results for several reasons. First, the severity of pruritus does not necessarily correlate with the severity of clinical disease. Many dogs are ineffective scratchers who may be very pruritic as perceived by the owners but cause few lesions. Secondly, the investigator was observing chronic dermatologic changes on many dogs that would not have changed much over a 6-week period while pruritus would change quickly. Finally, the purpose of this study was more to determine if there was a positive drug (marine oil) effect over time compared to the control then to compare absolute values of the different parameters to the other group or other parameters.

The side effects of high-dose EPA supplementation in this study were minimal. One dog had persistent vomiting and another acquired a "fishy" odor associated with the marine oil supplement. Both returned to normal once the supplement was discontinued.

The side effect of greatest concern with the use of high-dose EPA supplementation is a potential effect on normal platelet function (5, 26, 27). Numerous well-controlled double-blinded studies have been conducted on the effects of short-term (6–12 weeks) high-dose EPA supplementation on human platelet function both *in vivo* and *in vitro* (26). The results have been varied, with both significant and non-significant decreases of *in vitro* platelet function being reported, while significant increases in bleeding times were uncommon. In a double blinded study on 38 healthy dogs given short-term high-dose EPA supplementation (1.8 g of EPA orally q 24 h for 7 weeks) no significant increase in bleeding time was observed; no specific platelet function test were performed in this study (28). In the current study no clinical evidence of increased bleeding such as petechiae, ecchymoses, or gastrointestinal bleeding was observed although no bleeding times, activated clotting times or specific platelet tests were performed. Unfortunately, many cases of allergic skin disease in the dog require life-long anti-inflammatory therapy. It is, therefore, imperative that the long-term effects of high-dose EPA on platelets be investigated in dogs for which high-dose EPA supplementation is recommended for long-term use.

The increase in polyunsaturated fat and total fat in the diet may cause other potential side effects. Each capsule contains 1 g of oil which corresponds to approximately 9 calories. It is not known if over the long-term this will substantially increase the weight of the patient. The increased fat ingestion may also put animals with a tendency toward pancreatitis in jeopardy. Finally, the increased polyunsaturated fats may cause a decrease in vitamin E levels by increasing the rate and amount of oxidation. These side effects can be guarded against by using a lower fat maintenance diet and using a lower fat maintenance diet and using vitamin E as an antioxidant in the capsules themselves.

From this study it is evident that high-dose marine oil supplementation is an effective and apparently safe alternative to glucocorticoids for short-term relief of the symptoms of canine allergic skin disease. Before it can be recommended for long-term use,

studies of its effects on platelet function and on dogs predisposed to pancreatitis must be completed.

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Zusammenfassung—Ziel dieser Doppelblindkreuzstudie war die Untersuchung von Wirkungen der Substitution mit marinem Öl mit hohem Gehalt an Eicosapentensäure (EPA) auf juckende Hautkrankheiten beim hund. Sechzehn Hunde, die die Studie vollständig durchliefen, litten unter klinischen Symptomen, die mit idiopathischem Pruritus, nachgewiesener Atopie und/oder Flohallergie verbunden waren. Jeder Hund erhielt nach dem Zufallsprinzip eine omega-3-Fettsäurekapsel (MVP: Meridian Veterinary Product; St. Augustine, FL, U.S.A.), die 1 ml von marinem Öl enthielt (180 mg EPA und 120 mg DHA) oder eine Kapsel, die 1 ml Pflanzenöl enthielt (570 mg Linolensäure und 50 mg gamma-Linolensäure) bei einer Dosierung von 1 Kapsel pro 4,55 kg Körpergewicht alle 24 Stunden über 6 Wochen. Nach einer dreiwöchigen Ausschwemmphase, in der keine Substitution verabreicht wurde, wurde jedes Tier für weitere 6 Wochen auf die andere Supplementation gesetzt. Hunde, die marines Öl erhielten, zeigten eine signifikante Besserung des Juckreizes ($P < 0{,}001$), der Selbsttraumatisierung ($P < 0{,}05$) und der Fellbeschaffenheit ($P < 0{,}01$) während des Untersuchungszeitraumes. Im Verglich zur Pflanzenölkontrolle über den Zeitraum besserte die Substitution mit marinem Öl signifikant den Juckreiz ($P < 0{,}02$), die Alopezie ($P < 0{,}05$) und die Fellbeschaffenheit ($P < 0{,}001$). Diese Studie zeigt die Wirksamkeit von hohen Dosen von marinem Öl als alternativen Entzündungshemmer bei juckenden Hauterkrankungen des Hundes. [Double-blinded crossover study with marine oil supplementation containing high-dose eicosapentaenoic acid for the treatment of canine pruritic skin disease (Doppelblindkreuzstudie über die Substitution mit marinem Öl mit hohem Gehalt an Eicosapentensäure für die Behandlung von juckenden Hauterkrankungen bei Hunden.) *Veterinary Dermatology* 1994; 5: 99–104].

Resumen—El objetivo de este estudio recíproco tipo doble-ciego era examinar los efectos del suplemento de aceite marino con dosis alta de ácido eucosapentanoico (EPA) en al enfermedad canina prurítica de la piel. Dieciséis perros fue completaron este estudio presentaban signos clínicos asociados con prurito idiopático, atopia confirmada y/o alergia a pulgas. Cada perro fue puesto al azar en una cápsula de ácido graso omega-3 (MVP: Meridian Veterinary Product; St. Augustine, FL, U.S.A.) fue contenía 1 ml de aceite marino (180 mg EPA y 120 mg DMA) o una cápsula que contenía 1 ml de aceite de maíz (570 mg ácido linoleico y 50 mg ácido gamma linolénico) por 4,55 kg de peso corporal, 24 horas durante 6 semanas. Después de un periodo de 3 semanas durante el cual no se dió ningún suplemento, cada sujeto fue cambiado al otro suplemento por un periodo adicional de 6 semanas. Los perros que recibieron aceite marino mostraron una mejora significante en el prurito ($P < 0{,}001$), auto-trauma ($P < 0{,}005$) y carácter de la capa ($P < 0{,}01$) a lo largo del tiempo. Cuando se comparó al control del aceite de maíz a lo largo del tiempo, el suplemento de aceite marino mejoró significantemente el prurito ($P < 0{,}02$), alopecia ($P < 0{,}005$) y carácter de la capa ($P < 0{,}001$). Este estudio demuestra la efectividad de dosis altas de aceite marino como una alternativa antiinflamatoria para la enfermedad canina prurítca de la piel. [Double-blinded crossover study with marine oil supplementation containing high-dose eicosapentaenoic acid for the treatment of canine pruritic skin disease. (Estudio recíproco tipo doble-ciego con suplemento de aceite marino que contiene una dosis alta de ácido eucosapentanoico para el tratamiento de la enfermedad canina prurítica de la piel.) *Veterinary Dermatology* 1994; 5: 99–104].