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Scientific Article

Clinical efficacy and tolerance of an extract of green-lipped mussel (*Perna canaliculus*) in dogs presumptively diagnosed with degenerative joint disease

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Abstract

AIM: To evaluate the efficacy and tolerance of an extract of green-lipped mussel (GLME) in the management of mild-to-moderate degenerative joint disease (DJD) in dogs.

METHODS: Eighty-one dogs presumptively diagnosed with DJD were treated orally daily with either GLME or a placebo for 56 days, in a double-blind, placebo-controlled study. In an uncontrolled open-label extension to the study, all dogs were treated with GLME for an additional 56 days (from Days 57–112). Clinical signs were subjectively scored by the owners, and findings of detailed musculoskeletal examinations were scored by one veterinarian. Efficacy was assessed from a qualitative comparison of the proportion of dogs with improved clinical signs, and a quantitative comparison of the scores of the musculoskeletal examinations, between groups. Haematological and biochemical analyses and reports by owners of possible adverse drug reactions were used to screen for evidence of toxicity.

RESULTS: There was close agreement between assessments by the veterinarian and owners. The clinical signs of DJD in both GLME-treated and placebo groups improved significantly over baseline by Day 28; this improvement continued over the entire course of the study. There were no significant differences between groups on Day 28. On Day 56, a higher proportion of dogs in the GLME-treated group had improved clinical signs (p=0.018), and GLME-treated dogs had marginally better (p=0.053) musculoskeletal scores than dogs in the placebo group. The differences between the groups were no longer apparent by Day 112, by which time the former placebo group had been receiving GLME for 56 days in the open-label phase of the study. The proportion of dogs in the former placebo group that had improved by Day 112 (29/32; 91%) was significantly greater (p=0.012) than the proportion improved at Day 56 (15/37; 41%). No signs of toxicity were apparent.

CONCLUSIONS AND CLINICAL RELEVANCE: GLME had a beneficial effect on the clinical signs of dogs presumptively diagnosed with mild-to-moderate DJD. Long-term therapy may be required before improvement is apparent.

KEY WORDS: *Green-lipped mussel extract, Perna canaliculus, degenerative joint disease, arthritis, dog*

Introduction

Degenerative joint disease (DJD) or osteoarthritis is the most frequently diagnosed arthropathy of animals (Pedersen et al 2000). The cause of DJD is unknown but numerous predisposing factors have been recognised. These include obesity, instability, laxity or malalignment of joints, trauma, excessive work, and genetic factors (Smith et al 1995, 2001; Pedersen et al 2000). The predisposing factors result in accelerated turnover of the articular cartilage matrix, which eventually leads to localised degeneration of articular cartilage, exposure and sclerosis of underlying bone, formation of osteophytes, and thickening of the synovia (Manley 1995; Pedersen et al 2000). Damage to the articular cartilage is mediated by cytokines, prostaglandins, proteinases and oxygen-derived free radicals (Manley 1995). Eventually, the cumulative damage to the joints leads to clinical signs such as unwillingness to exercise, restricted joint movement, pain, stiffness, lameness, and crepitation or joint thickening (Manley 1995; Pedersen et al 2000).

The diagnosis of DJD is based on the history and clinical signs, as well as radiography of affected joints. Radiography will not detect early cartilage degeneration but will reveal more advanced degenerative changes such as osteophyte formation, subchondral sclerosis, attrition of subchondral bone, joint deformity and subluxation (Pedersen et al 2000). In certain clinical presentations, other diagnostic steps such as evaluation of joint fluid, synovial biopsy and tests for rheumatoid factor are indicated to diagnose less common forms of joint disease such as septic arthritis, immune-mediated polyarthritis and rheumatoid arthritis. However, evaluation of synovial fluid *per se* does not have sufficient sensitivity or specificity to allow clinicians to reach a definitive diagnosis of DJD (Gibson et al 1999; Pedersen et al 2000).

Traditionally, treatment of DJD has centred on rest, controlled exercise, management of predisposing factors, and periodic use of non-steroidal anti-inflammatory agents to reduce synovial inflammation and pain (Manley 1995; Pedersen et al 2000). The search for compounds to relieve the symptoms and alter the course of osteoarthritis has ranged across a wide spectrum of botanical, zoological, chemical and manufactured materials. This search for compounds showing the ideal balance between efficacy, side-effects and cost continues unabated. Recently, there has been an upsurge in interest in chondro-protective agents and alternative therapies such as parenterally-administered polysulphated glycosaminoglycans, and a variety of dietary supplements including

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ANOVA	Analysis of variance
DJD	Degenerative joint disease
GLME	Green-lipped mussel extract
SD	Standard deviation

anti-oxidants, chondroitin sulphate, glucosamine, omega-3 fatty acids, milk protein concentrate, and GLME (De Haan et al 1994; Gingerich and Strobel 2003).

GLMEs are derived from the New Zealand green-lipped mussel (*Perna canaliculus*). Various types of GLME have been employed in the management of arthritis. These include stabilised freeze-dried powdered preparations of the mussel tissue and oily extracts. Some authors observed a beneficial effect of GLME on rheumatoid arthritis and osteoarthritis in humans (Gibson et al 1980; Gibson 2000) but others did not (Larkin et al 1985; Darlington and Stone 2001). In dogs, recent studies by Bui and Bierer (2001) demonstrated that the addition of a green-lipped mussel powder to a dry diet resulted in significant clinical improvement in arthritis by the end of 6 weeks of treatment. In contrast, a lower dose of green-lipped mussel powder did not result in clinical improvement in another study of arthritis in dogs (Dobenecker et al 2002).

The purpose of the placebo-controlled phase of the study presented here was to compare the efficacy of a GLME with a placebo in alleviating the clinical signs of mild-to-moderate canine DJD. A secondary objective was to evaluate the tolerance of the GLME by dogs. The objective of the open-label phase of the study was to provide the manufacturer of the GLME-containing product with commercially-relevant information on the efficacy of the product as perceived by pet owners.

Materials and methods

Dogs

The 81 dogs (43 in the treated group and 38 in the placebo group) used in the study were selected from lame dogs presenting over a 10-month period to the Veterinary Teaching Hospital, Massey University, Palmerston North, New Zealand, or to private veterinary clinics in the lower North Island of New Zealand. The dogs all had clinical histories consistent with DJD, including intermittent or continuous lameness, stiffness on rising, and difficulty walking up or down stairs. The dogs remained in their owners' care for the duration of the study. The study was approved by the Massey University Animal Ethics Committee, Palmerston North, New Zealand.

Diagnostic procedures

The dogs were confirmed as generally healthy, following physical examination and routine urine, haematological and biochemical analyses. All dogs underwent a musculoskeletal examination conducted by the same veterinarian, to identify the affected joint(s). Radiography was performed to help confirm the diagnosis of DJD and rule out other causes of lameness. Joint taps were not performed on the dogs selected into the study because the procedure was not considered to be clinically indicated. Specifically, the dogs did not have a history or clinical signs suggestive of polyarthritis or septic arthritis, and there are no known tick-borne arthroses in dogs in this geographic region.

Criteria for selection and allocation of cases

Dogs presumptively diagnosed with mild-to-moderate DJD of more than 1 month's duration were considered for inclusion. Results of musculoskeletal examinations were graded using a scale of 1–5 (score increasing with increasing severity) proposed by Holtsinger et al (1992) for each of five parameters: lameness, weight-bearing, joint mobility/palpation, willingness to hold up the contra-lateral limb, and pain (Table 1). Dogs were excluded if they had a score >4 in one or more of these lameness grading categories, or if they had clinical evidence of septic or immune-mediated arthritis, neurological disorders, bleeding disorders, or were pregnant. Dogs were also excluded if they had been treated with topical or systemic anti-inflammatory agents (including oral nutritional supplements containing GLME) within the previous 2 weeks, with intra-articular injections within the previous 3 months, or had undergone orthopaedic surgery of any type within the previous month.

Dogs entering the study were grouped according to the joint(s) primarily affected (hip, shoulder, stifle, or other) and randomly allocated to one of two groups, *viz* treatment with a product containing GLME, or treatment with a placebo.

Treatment

The GLME treatment (SF4 Dog; McFarlane Laboratories New Zealand Ltd, Auckland, NZ) contained 125 mg GLME per tablet, 52.86 mg brewer's yeast, 191.50 mg lactose and 10.64 mg tab-

Table 1. Grading scale used by a veterinarian to assess the severity of musculoskeletal dysfunction in dogs presumptively diagnosed with degenerative joint disease (modified from Holtsinger 1992).

Parameter	Grade	Signs/assessment
Lameness		
	1	Stands and walks normally
	2	Stands and walks normally, slight lameness at the walk
	3	Stands normally, severe lameness at the walk
	4	Abnormal posture when standing, severe lameness at the walk
	5	Reluctant to rise and will not walk >5 strides
Willingness to hold up contra-lateral limb		
	1	Readily accepts for >2 min
	2	Mild resistance, accepts for >1min
	3	Moderate resistance, replaces it in <30 sec
	4	Strong resistance, replaces it in <10 sec
	5	Refuses to raise contra-lateral limb
Weight-bearing		
	1	Normal weight-bearing
	2	Normal weight-bearing at rest, favours limb when walking
	3	Partial weight-bearing at rest and at the walk
	4	Partial weight-bearing at rest, non-weight-bearing at the walk
	5	Non-weight-bearing at rest and when walking
Pain		
	1	No pain elicited on palpation of affected joint
	2	Mild pain on palpation, e.g. turns head
	3	Moderate pain on palpation, e.g. pulls limb away
	4	Severe pain on palpation, e.g. vocalises, attempts to bite
	5	Will not allow examiner to palpate joint
Joint mobility/palpation		
	1	No limitation of joint motion, no crepitus
	2	Mild (10–20%) decreased range of motion, no crepitus
	3	Mild (10–20%) decreased range of motion, crepitus
	4	Moderate (20–50%) decreased range of motion, crepitus
	5	Severe (>50%) decreased range of motion, crepitus

leting aid (magnesium stearate, acacia and aerosil). The placebo contained the same ingredients except for the GLME which was replaced by dried fin-fish (McFarlane Laboratories Ltd), and was of similar size, shape, colour, and odour to the GLME treatment. Both types of tablet were provided in identical plastic screw-top bottles identified only by code numbers. Both tablets were of a size easy to administer, were highly palatable to the dogs, and were administered daily according to bodyweight, *viz* 5–15 kg (three tablets), 16–20 kg (five tablets), 21–25 kg (six tablets), 26–45 kg (eight tablets), and 46–65 kg (nine tablets). Owners recorded the treatment and any observations of note in a daily log. Treatment continued for 56 days. Owner compliance was checked by reviewing the daily log and counting the tablets remaining in the bottles at the end of the treatment period.

At the conclusion of the placebo-controlled study, the owners were offered an open-label extension to the trial during which all dogs were treated with the GLME-containing product for 56 days. Thus, at the conclusion of the open-label phase of the trial, half the dogs had received GLME for 112 days and half had received GLME for 56 days.

Clinical examinations and sampling

The dogs were evaluated by the same veterinarian prior to commencement of treatment and after approximately 28, 56, and 112 days. Assessments at those intervals included a general physical examination and a musculoskeletal examination, scored as described above.

Blood samples were collected prior to treatment and on Day 56, by cephalic or jugular venepuncture. Samples collected into tubes containing EDTA were used for a complete blood count, including numbers of platelets. Serum was harvested in plain blood collection tubes, for analysis of the concentrations of calcium, phosphorus, sodium, potassium, bicarbonate, chloride, urea, creatinine, bilirubin, cholesterol, total protein, albumin, and globulin; the anion gap and albumin/globulin ratio; and the activity of creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, amylase, and lipase. Urinalysis was performed on free-catch urine. All analyses were performed by a commercial animal health laboratory (Batchelar Animal Health Laboratory, Palmerston North, New Zealand), and data were compared to the established reference ranges of that laboratory.

Assessments by owners

The general health of the dogs (appetite, attitude, level of activity, faecal consistency, and the presence of vomiting or any other abnormalities) and severity of lameness were assessed by their owners on Days 0, 26, 52 and 112. These assessments were recorded on forms using visual analogue and ordinal grading scales. Owners were also asked for an overall assessment as to whether or not their animal's condition had or had not improved.

Musculoskeletal assessment by the veterinarian

The severity of each dog's musculoskeletal dysfunction was assessed in both quantitative and qualitative manners. The five musculoskeletal parameters considered were assessed in a standardised way at each examination and a score for each parameter was allocated (Table 1). The scores of the individual parameters were added to give a cumulative score for each musculoskeletal examination. The cumulative score at each assessment during the trial was used as the quantitative clinical assessment. At each examination, the quantitative clinical assessment was qualitatively categorised as 'improved' (i.e. cumulative score lower than previous examination) or 'not improved'. This qualitative clinical assessment was based on the change (if any) in the cumulative score over baseline (Day 0).

Assessment of tolerance

Tolerance of the treatment was assessed by a comparison of the owners' reports of any adverse effects of the GLME treatment and placebo, and a review of the haematological, serum biochemistry and urinalysis data.

Statistical analysis

All statistical analyses were performed using SAS for Windows, v6.12 (SAS Institute Inc, Cary NC, USA). The degree of agreement between the owners' assessments of improvement and the veterinarian's qualitative assessment of improvement on Days 0, 28, 56 and 112 were analysed using the Kappa statistic. The veterinarian's qualitative assessments of improvement of the two groups of dogs on Days 0, 28, 56 and 112 were compared using logistic regression.

The cumulative musculoskeletal scores of the two groups were compared over Days 0, 28, 56 and 112, using repeated measures analysis of variance (ANOVA). Only complete datasets from dogs that had been examined on all four occasions were used for this analysis. The distribution of the residuals was checked for normality and homogeneity of variance; these checks confirmed that the assumptions of ANOVA applied to the cumulative scores. Contrasts were used to test whether there was any significant change between successive observations.

Results

Case recruitment

One hundred and forty-two dogs were presented for this study and of these 84 met the inclusion criteria. Data from three of these were eventually excluded from analysis as one dog was diagnosed with osteosarcoma of the scapula towards the end of the trial and the owners of the other two dogs failed to comply with the experimental protocol. Thus, data from 81 dogs were included in statistical analyses.

The mean age of the dogs was 8.5 (SD 3.3) years and mean weight was 32.6 (SD 11.1) kg. There were 48 females (59%), and the most common breeds were Labrador Retriever (26%), German Shepherd dog (12%), Border Collie (11%), and Rottweiler (11%).

The majority of the 81 dogs included in the data analysis completed the study. Seven of the 81 dogs did not complete the study for the following reasons, but partial datasets from these dogs were available. Three dogs were euthanised during the study: a 13-year-old dog in the GLME-treated group and an 11-year-old dog in the placebo group were euthanised due to overall poor quality of life, and an 11-year-old dog in the placebo group was euthanised for renal failure. Two dogs in the GLME-treated group and two in the placebo group were formally withdrawn from the study. Of these four, one owner believed the treatment caused the dog's coat to smell (this dog was in the placebo group), one dog in the treated group required anti-inflammatory treatment, and two owners were unable to continue to participate in the study. Data were incomplete from another four dogs because one dog was not presented for examination on Day 28, one was not presented on Day 56, and two animals were not presented on Day 112.

The DJD of the dogs included in the study most frequently affected the hip joint (43%) followed by the stifle (16%) and shoulder (10%).

Agreement between assessments by the veterinarian and owners

Agreement between the owners' assessments of improvement and the veterinarian's qualitative clinical assessments was 78% on Days 28 and 56, and 91% on Day 112, when both groups were treated with the GLME-containing product. The corrected coefficient of agreement (Kappa) was 0.546 on Day 28, 0.547 on Day 56, and 0.698 on Day 112, and there was no sign of systematic bias.

Qualitative clinical assessment

Results of the qualitative clinical assessments are shown in Table 2. On Day 28, there was no significant difference between the proportion of dogs showing improvement in the GLME-treated and placebo groups. In contrast, on Day 56 a higher proportion of dogs in the GLME-treated group (28/42; 67%) showed improvement than in the placebo group (15/37; 41%, p=0.018). On Day 112, when all dogs had been receiving GLME for either 56 (former placebo group) or 112 days (former GLME-treated group), 29/32 (91%) dogs in the former placebo group and 29/37 (78%) dogs in the former GLME-treated group had improved (p>0.05). The proportion of dogs in the former placebo group that had improved by Day 112 (91%) was greater than the proportion that had improved in that group by Day 56 (41%) on the placebo treatment (p=0.012). In contrast, the proportion of dogs in the GLME-treated group that improved was not significantly different (p>0.05) at Days 56 and 112.

Quantitative clinical assessment

Complete datasets for the repeated measures ANOVA were available from 70 dogs (32 from the placebo group and 38 from the GLME-treated group). The cumulative scores from the musculoskeletal examinations of both groups improved significantly from Days 0 to 28 (Figure 1). Between Days 28 and 56, cumulative scores of the GLME-treated group improved significantly but those of the placebo group did not, resulting in a marginally significant (p=0.053) difference between the scores of the two groups on Day 56. Between Days 56 and 112, the cumulative scores of both groups improved significantly, and by Day 112 there was no longer a significant difference between the groups.

Tolerance

Evaluation of haematological, serum biochemical and urinalysis data in relation to the testing laboratory's reference ranges for each parameter did not demonstrate any evidence of toxicity. No adverse effects that were attributable to the GLME treatment were described by the owners or the veterinarian.

Table 2. Qualitative clinical assessment of the percentage of dogs that had or had not improved on a placebo or green-lipped mussel extract (GLME) treatment by Day 28 and Day 56 of the placebo-controlled phase of a trial.

Day		Placebo	GLME-treated
28			
	Improved	16 (42%)	19 (45%)
	Not improved	22 (58%)	23 (55%)
56[a]			
	Improved	15 (41%)	28 (67%)
	Not improved	22 (60%)	14 (33%)

[a] Placebo and GLME-treated groups differ significantly (p=0.018)

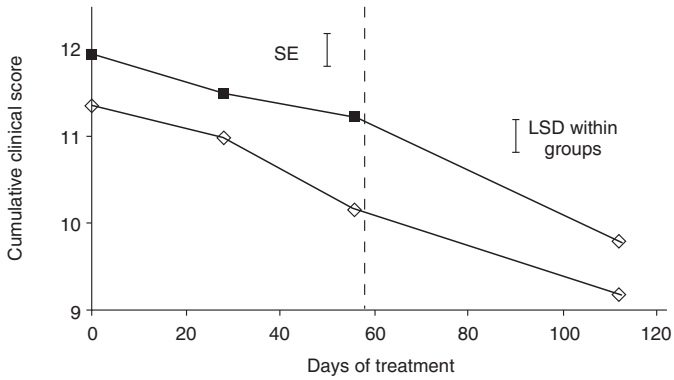

Figure 1. Cumulative musculoskeletal examination scores of dogs treated with either green-lipped mussel extract (GLME; ◇) or placebo (■) for 56 days, then with GLME for another 56 days. The standard errors (SE) for the individual datapoints were similar (0.37–0.43), and the pooled estimate (0.39) is shown here. There was a marginally significant (p=0.053) difference between the groups at Day 56. A least significant difference (LSD) bar is shown for comparisons between times within a group.

Discussion

The results of this study suggest that long-term administration, i.e. 8 weeks or longer, of GLME alleviated the clinical signs of dogs presumptively diagnosed with mild-to-moderate DJD. The reason for the lag period between the start of treatment with green-lipped mussel products and clinical improvement is unknown, but this has been reported previously (Bui and Bierer 2001).

The underlying process by which GLME has its beneficial effects on the clinical manifestations of DJD is unknown. Extracts of green-lipped mussel have been known for some time to have modest anti-inflammatory properties (Miller and Ormrod 1980; Rainsford and Whitehouse 1980; Couch et al 1982), and the active ingredient has variously been attributed to a proteinaceous macromolecule (Couch et al 1982), a prostaglandin inhibitor (Miller and Wu 1984), a glycogen extract or glycoprotein (Miller et al 1993), or a polyunsaturated fatty acid (Whitehouse et al 1997; Halpern 2000).

The high proportion of dogs (15/47; 41%) that improved in the placebo group during the first 56 days of the trial is noteworthy and similar to that seen in another recent trial of a nutraceutical in dogs with arthritis (Gingerich and Strobel 2003). The present trial was commenced in the middle of winter and most of the recruitment into the trial was completed within 6–9 months. Accordingly, some of the improvement seen in both the GLME-treated and placebo groups may be attributable to warmer weather conditions as the trial progressed. Increased focus by owners on appropriate rest, diet and exercise, factors already known to influence the course of DJD, may also have contributed to the improvement, as may have a 'placebo-like effect'.

The continued improvement of the musculoskeletal scores of the GLME-treated group during the open-label phase of the study may have been due to the prolonged duration of administration, which may have resulted in further clinical improvement. Alternatively, the perceived improvement may have been a placebo-like effect due to the 'unblinding' of the owners and veterinarian. Further research is required to establish the duration of treatment required for optimal therapeutic effect.

A high proportion of dogs in the placebo group improved from Day 56 (41%) to Day 112 (91%) after the placebo had been discontinued and replaced with open-label administration of the GLME. This particular comparison suggests that open-label administration of GLME to dogs with mild-to-moderate DJD is highly likely to produce a perceived beneficial clinical response, but does not separate placebo effects from direct effects of the GLME on DJD.

In conclusion, the results of this study suggest that the GLME-containing treatment used was well tolerated and had a significant beneficial effect on the clinical signs of dogs presumptively diagnosed with DJD, but that long-term therapy may be required before improvement is apparent.

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