Effectiveness of the Homeopathic Preparation Zeel Compared with Carprofen in Dogs with Osteoarthritis

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ABSTRACT

The authors compared the symptomatic effectiveness of a complex homeopathic preparation Zeel (1–3 tablets orally per day depending on body weight) to carprofen (4 mg/kg body weight) in dogs (n=68) aged >1 yr diagnosed with osteoarthritis in a multicenter, prospective, observational open-label cohort study in 12 German veterinary clinics. The active treatment period was 56 days. Symptomatic effectiveness, lameness, stiffness of movements, and pain on palpation were evaluated by treating veterinarians and owners. Clinical signs of osteoarthritis improved significantly ($P<0.05$) at all time points (days 1, 28, and 56) with both therapies. At the end of the treatment period, effectiveness was comparable in both groups. Both treatment regimens were well tolerated with only three treatment-related adverse events, all in the carprofen group. (*J Am Anim Hosp Assoc* 2011; 47:12–20. DOI 10.5326/JAAHA-MS-5483)

Introduction

Joint degeneration due to osteoarthritis (OA) is common in dogs. Clinical OA, the most common debilitating disease of mammalian joints, is reported to affect up to 20% of the canine population.[1] Progressive deterioration of articular cartilage, the hallmark of OA, in diarthrodial joints is characterized by hyaline cartilage thinning, joint effusion, and periarticular osteophyte formation. Clinical signs of OA include lameness, joint swelling, muscle atrophy, pericapsular fibrosis, crepitation, and pain.

Common therapies for OA include weight reduction, controlled exercise on soft surfaces, and pharmacologic treatment(s) to reduce pain and inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly used to reduce pain and suppress prostaglandin synthesis and subsequent inflammation. Some authorities recommend that treatment be limited to short-term use with both NSAID and corticosteroid therapies because of the risk for gastrointestinal (NSAIDs) and immunosuppressive and metabolic (corticosteroids) side effects in dogs.[2]

The increased interest in complementary and alternative medicine (CAM) in recent years has been noted not only in human practice but veterinary medicine as well.[3–5] One reason for this interest is a dissatisfaction with the tolerability profiles of many pharmacologic agents. Unfortunately, most CAM remedies have not been investigated in rigorous clinical trials resulting in a lack of evidence for the effectiveness of many popular medications.

Zeel[a] is a complex homeopathic preparation (available over-the-counter in Germany; prescription status varies between countries according to local regulations) based on highly diluted extracts from plants, animals, and minerals (sulfur) as well as defined biochemical substances including coenzyme A, DL-alpha-lipoic acid, sodium diethyl oxalate, and nicotinamide adenine dinucleotide. The precise composition of the Zeel tablets is described in **Table 1**. A number of studies have been performed on Zeel in human patients and the results indicate clinical benefits beyond what can be attributed to placebo effects. The reader is referred to a recent review for more detailed discussions of these

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CI *confidence interval;* AE *adverse event;* CAM *complementary and alternative medicine;* COX *cyclooxygenase;* ITT *intent-to-treat;* NSAID *nonsteroidal anti-inflammatory drug;* OA *osteoarthritis;* PO *per os;* PS *propensity score;* SC *subcutaneous;* SD *standard deviation;* SEM *standard error of the mean*

TABLE 1

Description of the Zeel Preparation Administered to Dogs with Osteoarthritis Included in this Study

Active component	Common name	Dilution*
Plant-derived ingredients		
Arnica montana	Mountain arnica	D4
Sanguinaria canadensis	Blood root	D4
Solanum dulcamara	Bittersweet	D3
Symphytum officinale	Comfrey	D8
Toxicodendron quercifolium	Poison oak	D3
Animal-derived ingredients		
Cartilago suis	Porcine cartilage	D6
Embryo totalis suis	Porcine embryo	D6
Funiculus umbilicalis suis	Porcine umbilical cord	D6
Placenta totalis suis	Porcine placenta	D6
Mineral and biochemical ingredients		
Coenzyme A		D6
DL-alpha-lipoic acid		D6
Nicotinamide adenine dinucleotide		D6
Sulfur		D6
Sodium diethyl oxalate		D6

*D2–D8, diluted 1:10 two to eight times

studies.[6] In addition to human use, Zeel has been successfully used in horses and rabbits.[7,8] In 2007, a double-blind study in canine OA indicated that the symptomatic benefits from Zeel were superior to placebo.[9]

To gather further data on the effectiveness of Zeel in dogs with OA, the authors conducted a study specifically comparing Zeel to the commonly used NSAID carprofen (Rimadyl[b]). Carprofen is an NSAID approved for the relief of pain and inflammation associated with osteoarthritis and surgery in dogs. The tolerability profile of carprofen in dogs is favorable, although, as with most NSAID, there is a risk of adverse effects (AEs) on the gastrointestinal, renal, and hepatic systems.[10] The goal of the study was to compare the symptomatic effectiveness of Zeel and carprofen in a varied population of dogs with OA in everyday veterinary practice.

Materials and Methods

Study Design

This was a multicenter, prospective, observational, nonrandomized cohort study conducted in 12 German veterinary clinics between October 2005 and July 2006. All animals were privately owned companion animals. The design and conduct of the study was in accordance with guidelines for Good Clinical Practice VICH GL9.[11] Participating clinics specialized either exclusively in CAM or conventional medical practice.

Included were dogs >1 yr diagnosed with OA but not currently undergoing treatment. Animals were included if they had clinical signs of lameness persisting for >3 wk and if the summary score of clinical signs at the initial veterinary examination was ≥4 points on the standardized evaluation scale (see below). Exclusion criteria included: dogs diagnosed with OA undergoing current therapy; prior surgery on the evaluated joint within 4 wk of enrollment; systemic or infectious disease; NSAID therapy within ≤1 wk of the beginning of the study; lameness of neurologic etiology; lameness from articular infection; fracture, musculoskeletal disease, or recent trauma requiring surgery; any neurologic deficit; previous treatment with phytotherapeutics; current use of feed additives with possible effects on joints or mobility; glucocorticoid treatments within ≤4 wk of the beginning of the study; and contraindication to any of the study therapies as described on the respective product information sheets.

Treatments

Animals were administered either carprofen (4 mg/kg PO *q* 24 hr for 56 days) or Zeel (1–3 tablets per os [PO] depending on body weight). Small dogs (up to 10 kg) were administered 1 tablet, medium-sized dogs (up to 20 kg) were administered 2 tablets, and large dogs (>20 kg), were administered 3 tablets) *q* 8–12 hr for 56 days. There was no randomization of therapy and the choice was at the discretion of the treating veterinarian. Both study medications were primarily administered as tablets, but there was an option to administer Zeel either subcutaneously (SC) or as a periarticular injection on days 1, 3, 14, and 28 and to administer carprofen (50 mg/mL SC) at the same time points. These injections were permitted to adjust the treatment doses during the course of the study at the discretion of the treating veterinarian.

Concomitant use of medications for OA such as NSAIDs (in addition to the carprofen), corticosteroids, or any similarly indicated CAM medications, was not allowed. There was no standardization of animal diets.

Study Duration and Evaluation

Dogs were treated daily for 56 days and were followed for a total of 70 days. At the start of treatment, the veterinarian collected clinicopathologic data including age, weight, sex, history of disease, number of affected joints, duration of disease, previous or concomitant diseases, and current medications. Efficacy was evaluated by the treating veterinarian on days 1, 28, 56, and 70. Owners assessed effectiveness on days 1, 56, and 70. Furthermore, an assessment of overall effectiveness was performed jointly by both the veterinarian and owner on day 56.

The effectiveness of the treatments was assessed by the veterinarian as the change in three main variables: lameness, stiffness of movements, and pain on palpation. Lameness was graded according to the European Agency for the Evaluation of Medicinal Products lameness score for dogs: 0 (normal, no lameness); 1 (slight, lameness visible, but dog unconcerned and exercises normally; 2 (moderate, obvious lameness present all of the time, dog having some difficulty with exercise; 3 (severe, dog barely weight bearing/not weight bearing.[12] Stiffness of movements was graded as: 0 (normal gait and step length and no arching of back); 1 (mild, slight disturbance of gait and step length and/or slight arching of back); 2 (moderate disturbance of gait and step length and/or moderate arching of back); and 3 (severe disturbance of gait, extreme reduction in step length and/or marked arching of back).[13] Pain on palpation was graded according to the European Agency for the Evaluation of Medicinal Products score: 0 (normal, no response to firm pressure); 1 (slight, digital pressure at site of lesion induces slight avoidance movement); 2 (moderate, digital pressure at site of lesion induces definite limb withdrawal); and 3 (severe, attempted digital pressure induces marked withdrawal).[14] All participating veterinarians received instruction and training on the scoring system before the beginning of the study.

The owners assessed their own animal's condition using the following parameters: willingness to play; willingness to walk, run, jump, and climb stairs; difficulty lying down; difficulty rising; stiffness after longer rest; and exercise intolerance. Each of these nine parameters was graded from 0 to 3 with 0 representing normal and 3 representing severely impaired conditions. The maximum possible score was 27. The joint evaluation of overall response to treatment performed by both the veterinarian and the owner on day 56 graded response to treatment using the following scale: 0 (excellent response, no detectable clinical signs); 1 (good response, marked reduction in clinical signs but not completely resolved); 2 (fair, clinical signs only slightly reduced); and 3 (poor, no improvement or worsened condition).

The primary effectiveness variable was the change from baseline in the sum of the three parameters (i.e., lameness, stiffness of movements, and pain on palpation) evaluated by the veterinarian. Secondary variables were the changes in the sum of the owner-assessed parameters, changes in individual parameters (judged by the veterinarians) and the overall treatment response at the end of the treatment (determined jointly by both the veterinarian and owner).

Tolerability was reported by the owners and assessed by the veterinarians, but not actively solicited, based on the occurrence of AEs. Treatment compliance was assessed by collecting and counting remaining tablets at the end of the study and results were expressed per animal as the percentage of the total number of tablets to be administered.

Statistical Methods

Data are given as means ± standard deviation (SD). A P value <0.05 was considered statistically significant. Least squares mean changes and 95% confidence intervals (95% CI) were calculated as appropriate. Standard statistical methods were used using SAS 6.12[c]. Treatment groups were compared using a two-way analysis of variance model for covariates based on interval data, the Cochran-Mantel-Haenszel test for ordinal data, and the Fisher's exact test for covariates with nominal values. Propensity score (PS) analysis was used to adjust for the groups not being statistically comparable for certain variables at baseline.[15,16] Dogs were stratified according to PS based on all baseline variables to construct matched strata that balanced observed covariates. The per-protocol population defined as all animals compliant to ≥80% after per-protocol population was used for the effectiveness analyses. For the safety analysis, the entire study population was used. A complementary effectiveness analysis was conducted on the intent-to-treat (ITT) population comprising all enrolled animals including the protocol violators. For the comparison between treatments, noninferiority of Zeel to carprofen was assessed on the primary effectiveness variable and on the veterinarian-assessed individual variables. The noninferiority analysis compared the lower border of the 95% CI for the differences in change between the treatments groups. The noninferiority limits were set to 1.5 units for the differences between the primary effectiveness variable (the summary score for the 3 veterinarian-evaluated variables) and to 0.5 units for all secondary effectiveness variables. This was not a confirmatory study and thus every individual efficacy and safety criterion was assessed.

Results

Study Populations

A total of 68 dogs were enrolled into the study: 37 in the Zeel group and 31 in the carprofen group. Two dogs in the Zeel group and three dogs in the carprofen group were excluded from the per-protocol analysis because of protocol violations (premature discontinuation of therapy) and one dog in the Zeel group was excluded for reasons of noncompliance. Thus, the per-protocol analysis of effectiveness was conducted on 62 animals: 34 receiving Zeel and 28 receiving carprofen. The mean duration of therapy was 57.5 days in both groups and the veterinary examinations were conducted on the median days of treatment (first–third quartiles): 15 (14–16), 29 (28–30), 57 (56–59), and 71 (70–76) as well as the examination performed at baseline (day 1).

The two populations were balanced at baseline (**Table 2**) with some exceptions. Before PS adjustment, owner-evaluated disease scores were significantly lower in the Zeel group than in the carprofen group although veterinarian-evaluated scores did not differ significantly between the two groups. More animals in the Zeel group than in the carprofen group (26% versus 11%) presented with >1 diseased joint (P=0.0451 before adjusting for PS). In both treatments groups, the hip and elbow were the most commonly affected joints: 55% of all animals had diseased hips and 27% diseased elbows (data not shown). All baseline differences mentioned above were successfully adjusted for by PS analysis.

More animals in the carprofen group than in the Zeel group had received previous therapy for OA. The most common previous therapy was carprofen which had been used in 24% of dogs in the Zeel group and 29% of dogs in the carprofen group. Meloxicam[d] was the second most common previous therapy and had been administered to 6% of animals in the Zeel group and 36% of those in the carprofen group. No other therapy had been used in >1 animal in either group prior to enrollment to the study.

The use of concomitant therapies was low in both groups. The most common concomitant medication was angiotensin-converting enzyme inhibitor therapy that was used in 3 dogs (9%) in the Zeel group and 5 dogs (18%) in the carprofen group. No other concomitant medication was used in >1 animal in either group.

Effectiveness

Both treatments reduced clinical signs of OA during the 70 day observation period (**Table 3**). The primary effectiveness variable, the summary score of the three veterinarian-assessed variables, was reduced in the Zeel group from 5.2 ± 0.9 at baseline to 2.3 ± 1.5 at the end of therapy. In the carprofen group, the summary score was reduced from 5.0 ± 1.1 at baseline to 2.0 ± 1.6 at the end of therapy. Compared with baseline, these reductions were significant (P<0.05) at all time points (**Figure 1**). During the 14 day observation period between the end of active treatment and the final examination, dogs in the Zeel group demonstrated a further slight reduction to 1.9 ± 1.3. In contrast, there was an increase in the summary score in the carprofen group during this same period to 3.0 ± 2.2.

The changes in the variables making up the effectiveness score (**Figure 2**) indicated that Zeel had greater effects than carprofen on pain on palpation during the active treatment period whereas carprofen appeared to be more effective on the variables lameness and stiffness with movement. During the 14 days between the end of therapy and the final observation, the score reductions were maintained or increased in the Zeel group. In the carprofen

TABLE 2

Demographic Data Collected at Baseline (Per-Protocol Population)

Characteristic	Zeel group (n=34)	Carprofen group (n=28)	*P* value*
Age yr ± standard deviation	7.6 ± 3.5	10.2 ± 3.3	0.6063
Weight kg ± SD	33.3 ± 15.9	30.7 ± 11.9	n.s.
Male sex %	56	57	n.s.
Castrated %	59	57	n.s.
Estimated duration of OA, years ± SD	1.8 ± 1.6	1.7 ± 1.7	n.s.
Number of affected joints %			
1	74	89	0.1526
≥2	26	11	
Affected joints† %			
Hip	65	43	0.1432
Elbow	26	29	n.s.
Veterinarian-evaluated disease score mean ± SD§ (maximum score=9)	5.2 ± 0.9	5.0 ± 1.1	n.s.
Owner evaluated disease score mean ± SD§ (maximum score=27)	10.3 ± 4.3	13.3 ± 4.4	0.5164
Previous treatment of OA %	51	84	0.2351
Concomitant therapy during study %	24	35	0.4921

**P* value for differences between groups after adjustment for propensity score (PS). Note that n.s. indicates that there were no significant differences before PS adjustment and no such adjustment was done to these variables in the table. Weight P=0.4718, male sex P=1.000, castrated P=1.000, duration of illness P=0.7864, affected joints (elbow) P=1.000

†Multiple entries possible

§Severity of individual clinical signs was graded on a score from 0 (normal) to 3 (severe).

SD, standard deviation

TABLE 3

Effectiveness Variables at Baseline (Day 1) and on Days 28, 56, and 70 of the Study

	Day 1 (baseline)		Day 28		Day 56 (End of treatment)		Day 70 (End of study)	
Variable	Zeel group (n=34)	Carprofen group (n=28)	Zeel group (n=34)	Carprofen group (n=28)	Zeel group (n=34)	Carprofen group (n=28)	Zeel group (n=34)	Carprofen group (n=28)
Veterinarian-evaluated score mean ± SD* (maximum score=9)	5.2 ± 0.9	5.0 ± 1.1	2.8 ± 1.3	2.1 ± 1.3	2.3 ± 1.5	2.0 ± 1.6	1.9 ± 1.3	3.0 ± 2.2
Lameness	1.5 ± 0.6	1.6 ± 0.6	0.6 ± 0.7	0.7 ± 0.7	0.6 ± 0.7	0.6 ± 0.7	0.4 ± 0.7	1.0 ± 0.9
Stiffness of movements	1.8 ± 0.5	2.0 ± 0.7	1.0 ± 0.6	0.7 ± 0.5	0.7 ± 0.7	0.7 ± 0.7	0.6 ± 0.6	1.0 ± 0.9
Pain on palpation	1.9 ± 0.5	1.4 ± 0.8	1.2 ± 0.6	0.8 ± 0.6	0.9 ± 0.5	0.7 ± 0.7	0.9 ± 0.5	0.9 ± 0.8
Owner-evaluated score mean ± SD* (maximum score=27)	10.3 ± 4.3	13.3 ± 4.4			6.0 ± 4.2	7.2 ± 5.0	6.0 ± 5.0	9.1 ± 5.0
Willingness to play	0.9 ± 1.0	1.5 ± 1.1			0.6 ± 0.8	0.9 ± 1.0	0.5 ± 0.7	1.1 ± 1.0
Willingness to walk	0.6 ± 0.6	1.0 ± 0.9			0.3 ± 0.5	0.4 ± 0.5	0.3 ± 0.5	0.6 ± 0.7
Willingness to run	0.9 ± 0.7	1.4 ± 1.0			0.4 ± 0.5	0.8 ± 1.0	0.4 ± 0.6	1.1 ± 1.1
Willingness to jump	1.5 ± 0.9	2.0 ± 1.2			1.2 ± 1.1	1.4 ± 1.3	1.1 ± 1.1	1.4 ± 1.2
Willingness to climb stairs	1.2 ± 1.0	1.4 ± 1.0			0.7 ± 0.9	0.8 ± 0.6	0.8 ± 0.9	1.3 ± 1.1
Difficulty in laying down	0.9 ± 0.8	0.9 ± 0.8			0.4 ± 0.6	0.5 ± 0.7	0.4 ± 0.7	0.5 ± 0.7
Difficulty in rising	1.4 ± 0.8	1.7 ± 0.6			0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.7	0.9 ± 0.9
Stiffness after longer rest	1.4 ± 0.7	1.9 ± 0.4			0.8 ± 0.6	0.8 ± 0.8	0.9 ± 0.8	1.2 ± 0.9
Exercise intolerance	1.5 ± 0.7	1.4 ± 0.9			0.8 ± 0.7	0.9 ± 0.7	0.8 ± 0.6	1.0 ± 0.9

*Severity of each individual clinical sign was graded on a score from 0 (normal) to 3 (severe).
SD, standard deviation

group, the reductions in the scores for all three variables decreased with time after the end of treatment. The sample sizes and the design of the study did not include statistical assessments of such differences on individual variables at different time points.

Similar observations of greater initial reductions with carprofen therapy but more sustained improvements over time with Zeel treatment were made for the owner-assessed effectiveness scores. Overall summary scores as well as individual scores were reduced with active treatment in both treatment groups (Table 3). Between the end of therapy and the end of the observation period, the Zeel effectiveness scores were either stable or reduced further. In the carprofen group, effectiveness scores trended toward a return to the baseline values. This lack of sustainability was most pronounced for the variables willingness to run and willingness to climb stairs. The changes from baseline at the end of the study were greater with Zeel treatment, whereas at day 56, the changes were greater in the carprofen group (**Figure 3**).

The noninferiority analysis of the primary effectiveness variable (**Figure 4A**) showed that although there was a trend toward greater effectiveness with carprofen at day 28 and at the end of the active treatment period, the differences did not reach the predefined clinically relevant border for inferiority. Thus, it was concluded that Zeel was noninferior to carprofen in this analysis. Repeating the analysis in the ITT population yielded similar results as the per-protocol analysis and the noninferiority of Zeel was confirmed in this population.

As a consequence of the differences in sustainability of therapeutic effects, the differences between the groups at day 70

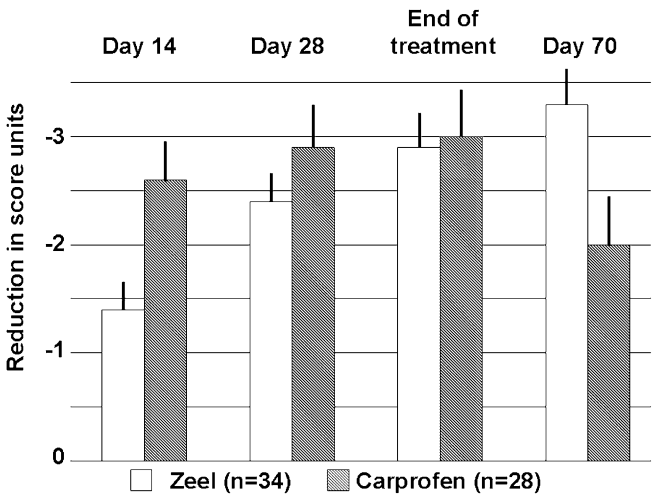

FIGURE 1 *Change from baseline to different time points during the study in the primary effectiveness end point. Scores are given as negative values; greater change (reduction in score units) indicates greater improvement. Lines represent standard error of the mean (SEM).*

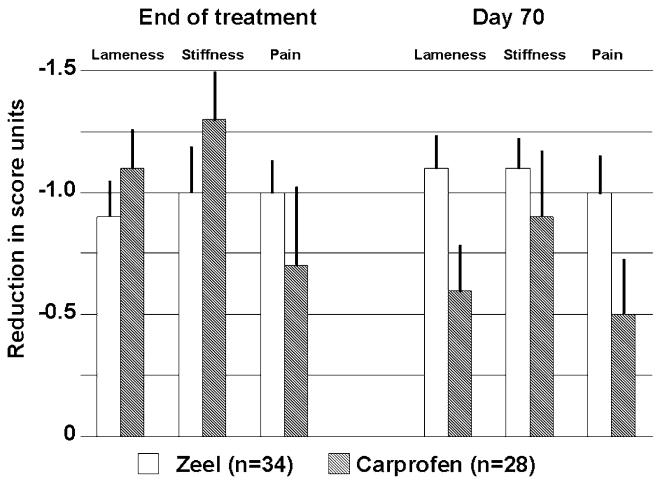

FIGURE 2 *Changes from baseline to different time points during the study in the individual variables making up the primary effectiveness end point. Scores are given as negative values; greater change (reduction in score units) indicates greater improvement. Lines represent standard error of the mean (SEM).*

were in favor of dogs that had been treated with Zeel. The lower border of the 95% confidence interval for differences between treatments at day 70 crossed the line of unity indicating that the differences in favor of Zeel at this time point were not statistically significant; however, no analysis had been prespecified to determine possible superiority of Zeel at any time point. An analysis of the three components of the overall effectiveness score showed similar results for all three scores as for the overall score (**Figure 4B**), with the score for lameness on day 70 indicating superiority of Zeel compared with carprofen. This trend toward greater benefits from Zeel with time was also observed in the complementary ITT analysis.

The joint evaluations of effectiveness at the end of the treatment phase on day 56 were similar in both treatment groups (**Figure 5**). Veterinarians assessed effectiveness as excellent or good in 74% of Zeel cases and in 79% of carprofen cases, respectively. Similarly, owners reported excellent or good global effectiveness in 67% and 75% of Zeel and carprofen cases, respectively.

Tolerability

Both treatment regimens were well tolerated. In the Zeel group, no treatment-related AEs were reported (total number of AEs reported was five). In the group receiving carprofen, 11 AEs were reported in total. Of these, three (one case each of enteritis, acute arthritic attack, and apathy) were considered treatment-related. Two dogs in the Zeel group and one dog in the carprofen group died during the course of the study; however, none of these deaths was considered treatment-related.

Discussion

The results of this observational pilot study indicate that the effectiveness of Zeel is noninferior to the NSAID carprofen in dogs with OA over a treatment period of 56 days. The veterinarian-assessed effects of Zeel were sustained for an additional 2 wk after the end of the active therapy, whereas the effects of carprofen trended to return toward baseline values during the posttreatment phase of the study. The changes in owner-evaluated effectiveness at

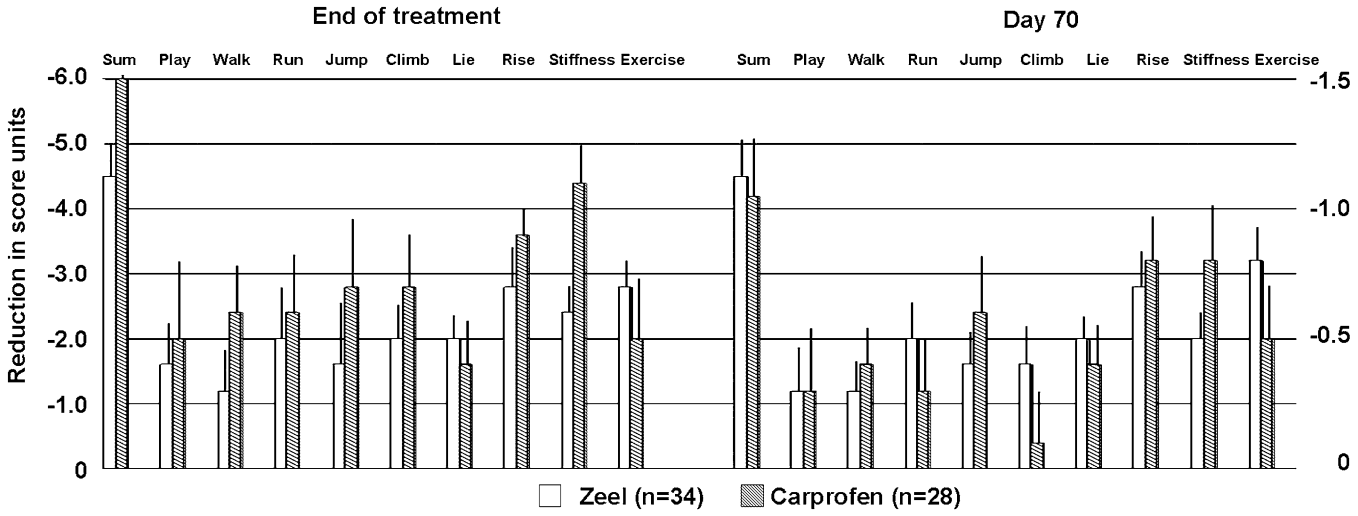

FIGURE 3 *Changes from baseline in owner-assessed scores for effectiveness at end of treatment and end of the observation period (day 70), respectively. The bars representing overall scores ('sum') refer to the right-hand scale; all other bars refer to the left-hand scale. Scores are given as negative values; greater change (reduction in score units) indicates greater improvement. Lines represent standard error of the mean (SEM).*

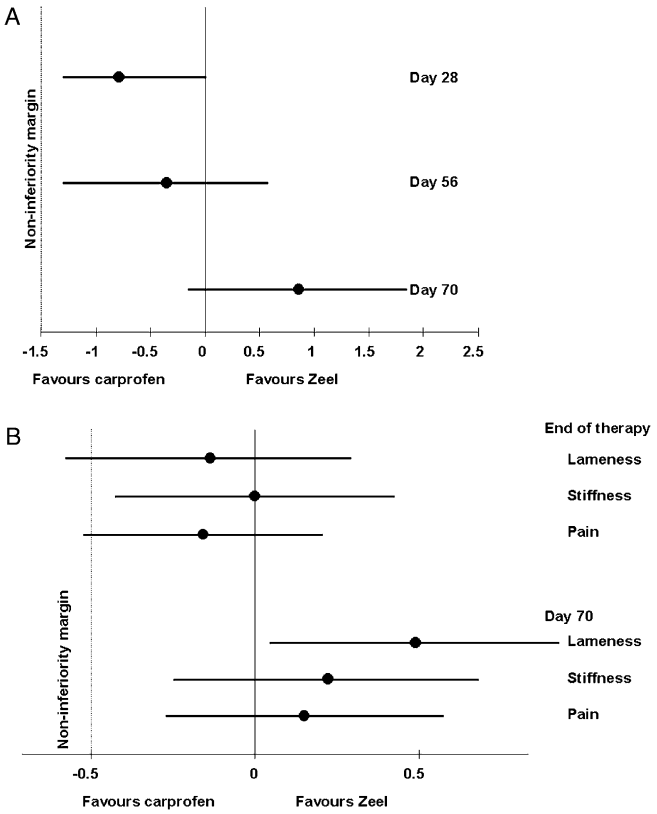

FIGURE 4 A*: Noninferiority analysis for the primary effectiveness variable at days 28, 56, and 70. The dotted line represents the margin of noninferiority of Zeel therapy to carprofen therapy: -1.5 points on the summary score for veterinarian-assessed effectiveness.* B*: Noninferiority analysis for the individual components of the primary effectiveness variable at days 56 and 70. The dotted line represents the margin of noninferiority of Zeel therapy to carprofen therapy: -0.5 score points.*

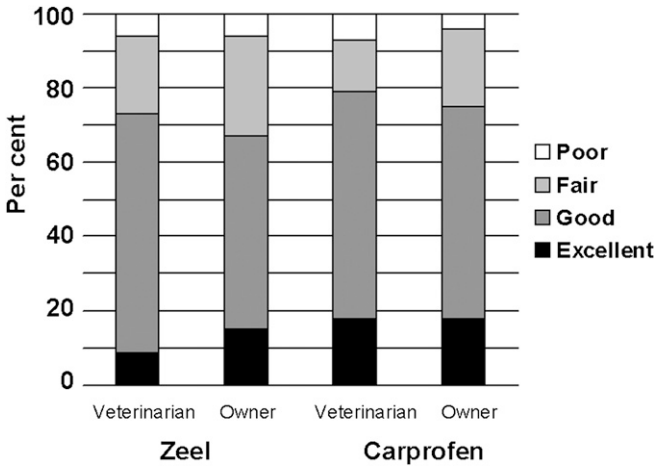

FIGURE 5 *Joint evaluation of effectiveness at the end of therapy (day 56) by veterinarians and dog owners. The values are the percentages of respondents for each degree of effectiveness.*

the end of therapy and end of study were similar to those assessed by veterinarians.

Carprofen has been used to treat OA in dogs for many years. In animals, carprofen appears to be more potent than aspirin and with a more favorable safety profile.[17] Zeel is a complex homeopathic preparation based on extracts from plants, animal tissues, and minerals in combination with defined biochemical substances, all at high dilutions. The observed noninferiority of this therapy might carry implications for the usefulness of Zeel in the treatment of canine OA and it indicates that the preparation is worthy of further study.

Some weaknesses of the analysis should be noted. This was a nonrandomized observational study with no blinding of participating doctors and owners. Yet, at least for the dog owners, the desire to see improvements should be equally great in both treatment groups with no reason to suspect bias. The study sample was relatively small but in accordance with other studies on dogs with OA.[13,18] The treatment groups differed at baseline in some regards, which is common in nonrandomized cohort studies and several statistical methods have been developed to correct for variations between covariates. In the current study, all could be adjusted for by PS analysis. The design lacked a placebo group and thus it was not possible to address the questions of placebo effects or regression to the mean. As dogs were permitted into the study with a clinical history of lameness for 3 wk, some improvement in both treatment groups might be attributable to the natural course of the disease. The exclusion criterion that any joint surgery occurred more than 4 wk prior to the start of the study meant that some dogs might have undergone surgery fairly recently. Such patients may improve postoperatively without any adjunctive treatment, but to influence the results would have taken a substantial number of such patients, which appears unlikely. The disparity in the numbers of animals between the two groups is common in nonrandomized studies capturing clinical practice and there is no reason why it should influence the outcomes.

Further, the scoring system has not been scientifically validated and some outcomes measurements are subjective. In the absence of standardized assessment methods for noninferiority of therapies in this indication and treatment population, the border of the noninferiority analysis was, by necessity, set somewhat arbitrarily, yet at a clinically relevant level. It should also be noted that the variables used to assess effectiveness have no standardized scale and assessment might vary slightly between observers. Nonetheless, the reported findings are supported by a recently published double-blind study in canine OA indicating that both Zeel and carprofen are superior to placebo.[9] Although the design (notably

once daily Zeel dosing in the double-blind study), study variables, and analysis differed from the current study and there was no formal comparison between Zeel and carprofen, the results from both studies are consistent.

There is an increased interest in the use of CAM therapies in veterinary practice. The term CAM covers a large variety of different approaches: popular remedies for OA in animals include antioxidant vitamins C and E, preparations such as chondroitin sulfate and glucosamines, and omega-3 fatty acid supplements.[5] Few CAM remedies have been subjected to rigorous scientific studies.[19] By contrast, there is a growing body of evidence supporting the effectiveness and specific modes of action for Zeel, although more and larger studies would clearly be desirable. In humans with OA, Zeel has been shown to be similarly effective to the NSAID diclofenac and to hyaluronic acid in two separate randomized double-blind studies.[20,21] A large-scale observational study also indicated comparable effectiveness of Zeel and cyclooxygenase (COX)-2 selective agents in patients with OA of the knee.[22] In vitro assays indicate that Zeel has inhibitory effects on COX-1 and COX-2 and a dose-dependent inhibition of prostaglandin E2 has been demonstrated with reconstituted Zeel in cell cultures.[23] There is no reason to believe that the molecular mechanisms underlying the effectiveness of Zeel in OA differ between species. Recent molecular data have shown that the changes in patterns of gene expression in naturally occurring canine OA are broadly similar to those reported in the human disease.[24] In vitro experiments have indicated growth-promoting effects on human chondrocytes with Zeel, a phenomenon that deserves further investigation.[25]

The inclusion of a 2 wk washout period in the study design provided insights into the sustainability of the respective therapies. The beneficial effects in the Zeel group were sustained or even increased during the 14 day posttreatment observation period whereas there was a reduction in effectiveness scores in the group of dogs that had received carprofen. The differences were most marked for the veterinarian-assessed scores and were similar for all three subscores. Similar but less pronounced trends were present in the owner-assessed scores. It is conceivable that some of the effectiveness variables reflect behaviors more strongly related to acute analgesic effects from therapies while others reflect behaviors more closely related to systemic changes over longer duration. Such a hypothesis is supported by the observation that the effects of Zeel were less marked at the early examinations (day 14 and day 28) but increased during the course of the study. This is in contrast to the effects of carprofen which were observable as early as day 14 but increased less with time than the effects of Zeel. Although the veterinarian-assessed scores indicated that the effects of Zeel on pain were greater than those of carprofen at the end of treatment, the pain score on days 14 and 28 was no better than carprofen (data not shown). This might further support the possibility of effects of Zeel therapy beyond direct and immediate analgesic effects. It would be interesting to monitor the effects of Zeel therapy over extended time spans. The observational design of the current study constrains the analyses that can be done on comparisons between treatments and a specifically designed trial would be needed to address this issue.

Both treatments were well tolerated although there was a trend toward more treatment-related AEs with carprofen. This observation is in agreement with the generally better safety profile of homeopathic preparations, including Zeel, compared with NSAIDs.[6] From the current study with its limited size of study population and its midterm nature of the therapeutic regimens, the occurrence of AEs related to long-term use cannot be evaluated.

Conclusion

This observational pilot study indicates that the effectiveness of the homeopathic combination therapy Zeel is noninferior to that of the commonly used canine NSAID carprofen for the medium-term symptomatic treatment of dogs with OA. The clinical usefulness of Zeel over longer periods of treatment, claimed by veterinary clinics practicing CAM, deserves further investigation.

Financial support for the study was provided by Heel GmbH, Baden-Baden, Germany.

FOOTNOTES

[a] Zeel; Biologische Heilmittel Heel GmbH, Baden-Baden, Germany

[b] Carprofen (Rimadyl); Pfizer Animal Health, Exton, PA

[c] SAS 6.12; SAS Institute Inc. Cary, NC

[d] Meloxicam (Metacam); Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MS

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