

A multicentre clinical study of the efficacy of sodium pentosan polysulfate and carprofen in canine osteoarthritis (osteoarthrosis)

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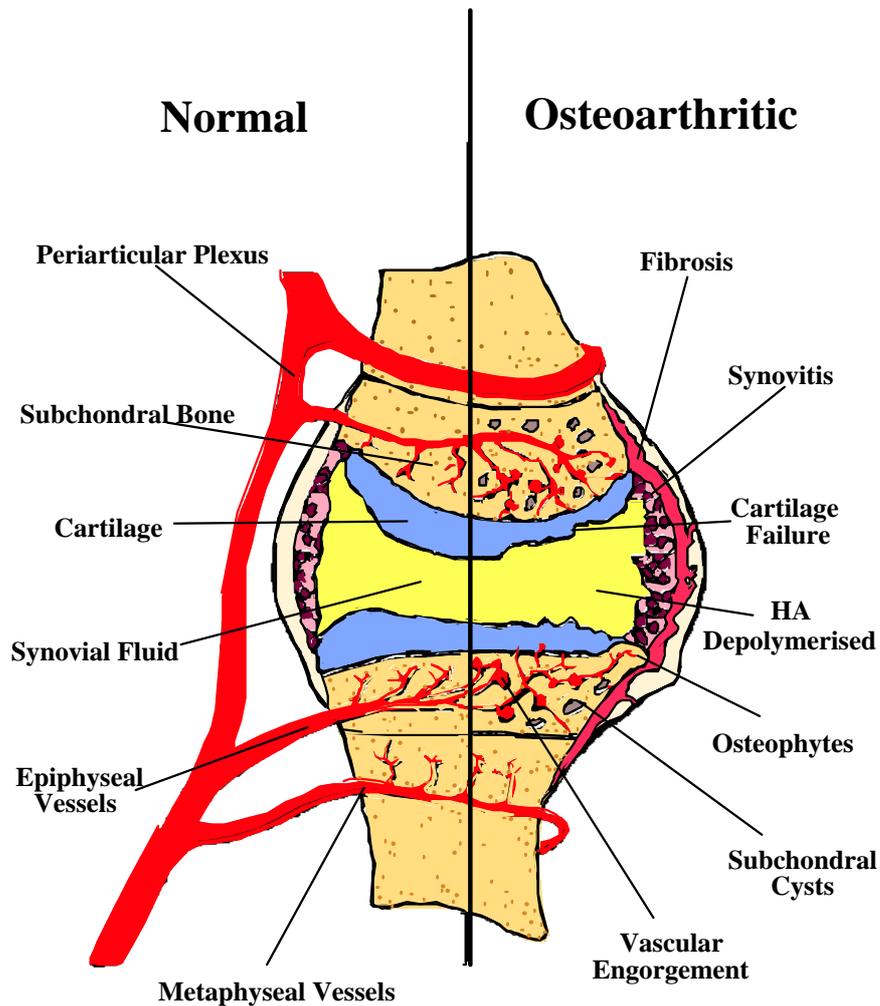
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One hundred and four dogs diagnosed with osteoarthritis (OA) were enrolled in a multi-centre, double-blind, comparator controlled, randomised clinical study in Germany to establish the effectiveness of the disease modifying anti-osteoarthritic drug, sodium pentosan polysulfate (NaPPS - marketed as *CARTROPHEN VET*[®]) compared to the non steroidal anti-inflammatory control drug carprofen (Rimadyl[®], Zenecarp) in treating the clinical signs of OA. Efficacy was assessed by a reduction in the clinical signs of OA, namely lameness and pain on manipulation by the veterinarian during treatment (Weeks 1, 2, 3 and 4) and four weeks after treatment had ceased (Week 8). Four weekly subcutaneous injections of NaPPS at 3mg/kg by the subcutaneous route and four week daily oral administration of carprofen at 4mg/kg were found to be effective in treating OA with significant improvements in all primary outcome parameters i.e. lameness, pain and orthopaedic score ($p < 0.05$). NaPPS maintained its effectiveness longer than carprofen with significant improvement following NaPPS treatment compared to carprofen treatment in orthopaedic score at Week 8 ($p = 0.013$).

Introduction

Osteoarthritis (OA) is a disorder which may affect all articulations but is most prominent in the spine and the peripheral weight-bearing joints [Felson, 1988; Altman, 1991; March and Brooks, 1996]. OA is characterised pathologically by focal fibrillation and erosion of articular cartilage, subchondral bone changes including sclerosis, osteolysis, osteophytosis and synovial inflammation [Gardner, 1983; Mankin, Brandt and Shulman, 1986; Ghosh, 1991; Hamerman, 1993] (see Figure 1). While the number of studies on the natural history of OA in the canine is limited [Van Pelt, 1965; McDevitt *et al.*, 1974; McDevitt and Muir, 1976; Alexander, 1979; Lust and Summers, 1981; Pederson, Pool and Morgan, 1983; Kealy *et al.*, 1997] there is a plethora of reports in the literature of canine arthropathies induced experimentally. The most widely used models have been the induction of traumatic OA in canine joints by meniscectomy [Cox *et al.*, 1975; Ghosh *et al.*, 1983a,b, 1984; Hannan *et al.*, 1987; Smith and Ghosh, 2001] or transection of the anterior cruciate ligament (ACL) [Sandy *et al.*, 1984; Altman *et al.*, 1984; Pelletier *et al.*, 1985; Dunham *et al.*, 1985; Fife, 1986; Johnson and Poole, 1990; Myers *et al.*, 1990; Brandt *et al.*, 1991a,b; Carney *et al.*, 1985, 1992; Ratcliffe *et al.*, 1993; Guilak *et al.*, 1994; Adams, 1994; Venn *et al.*, 1993, 1995; Dourado *et al.*, 1996]. The clinical outcome of experimental transection of the ACL mimic the naturally occurring situation [Elkins *et al.*, 1991; Vasseur and Berry, 1992]. Collectively, these studies have confirmed that the pathological and biochemical events which occur in synovium, cartilage and subchondral bone in canine OA parallels those described for human disease. Indeed, these canine models have been widely used to identify the molecular changes which occur in joint tissues during the inception and progression of OA. Moreover, these canine models of OA have been used for the evaluation of pharmacological agents which have been reported to modify pathobiological pathways considered implicated in the disorder [Pritzker, 1994]. The pool of knowledge which has accumulated on the composition, structure and function of human joint tissues in health and OA is thus a valuable reference source for evaluation of the corresponding canine disorder and vice-versa.

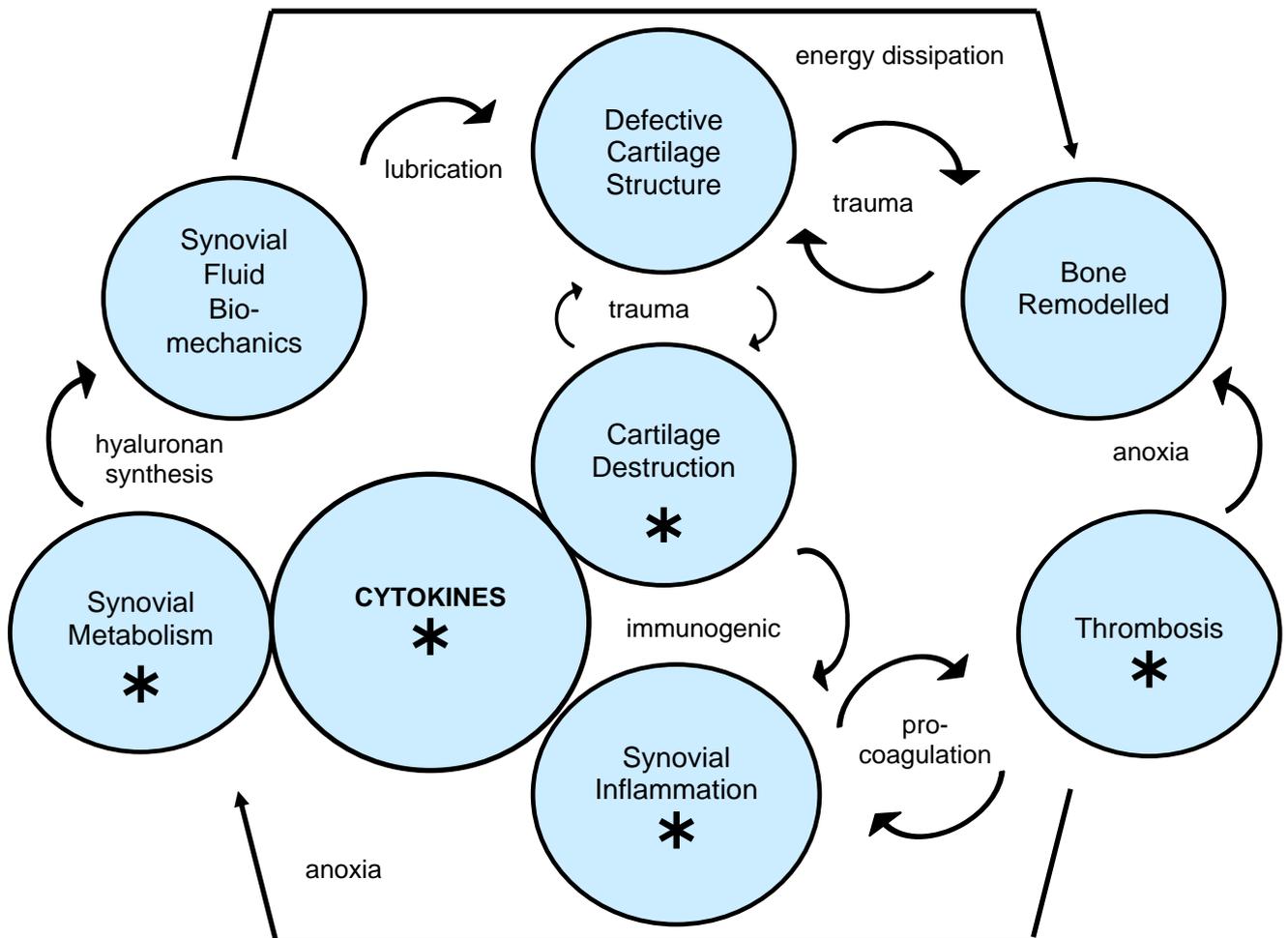
Figure 1: In osteoarthritic joints pathological changes occur in articular cartilage (loss of proteoglycans, fibrillation/erosion), subchondral bone (vascular engorgement, re-modelling, sclerosis, osteophytosis) and synovium (inflammation, fibrosis and abnormal hyaluronan (HA) synthesis).



Medical treatments for OA have, up until recently, targeted the clinical signs of the disease, rather than the underlying pathologies responsible. Analgesics and steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) are, and still remain, the mainstay of treatment [Brandt and Slowman-Kovac, 1986; Gabriel and Wagner, 1997; Johnston and Budsberg, 1997; Fox and Johnston, 1997]. However, the deleterious side effects provoked in dogs and humans with the use of many of these agents (*e.g.* on the gastrointestinal tract, kidneys and articular cartilage) [McKenzie *et al.*, 1976; Palmoski and Brandt, 1980; Innes, 1995; Lichenstein *et al.*, 1995; Manoukian *et al.*, 1996; Isaacs, 1996] has led to a steady decline in their usage in recent years. A variety of new compounds now marketed have been reported to be selective inhibitors of COX-2 at low plasma concentrations [Vane and Botting, 1996; Engelhardt, 1996; Noble and Balfour, 1996; Engelhardt *et al.*, 1995; Hulse 1998; McLaughlin, 2000]. While these new NSAIDs are reported to have diminished adverse side effects on the gastrointestinal tract they are still associated with other toxicities, which are now becoming more apparent as their clinical use increases. This is particularly evident for the kidney where COX-2 enzymes are expressed and have important physiological functions [Perazella and Tray, 2001]. In addition in the dog carprofen (Rimadyl[®]) is associated with liver toxicity [MacPhail *et al.*, 1998] in certain breeds. Moreover, there is no evidence that steroidal or NSAIDs provide any beneficial effects on the underlying haematological abnormalities which exist in OA joints, which can contribute not only to the clinical signs of the disorder but also its progression. Indeed chronic use of corticosteroids is known to exacerbate intravascular coagulation and osteonecrosis [Jones, 1993] and from this standpoint alone may contribute to disease progression.

One class of drugs, the pentosan polysulfates (PPSs) which have been actively researched for more than 40 years, have now been developed for the treatment of OA [Ghosh, 1999]. The disease modifying properties of PPS are outlined in Figure 2. Therapeutic intervention with sodium pentosan polysulfate (NaPPS) in the ACL deficient dog model of OA was shown to maintain cartilage structure and biochemistry [Rogachefsky *et al.*, 1993]. It was hypothesised that this effect was due to NaPPS's ability to block proteinase activity and that this allowed the observed growth factor induced effects. In a similar study in the dog knee model of disuse atrophy, Grumbles *et al.* (1995) speculated about the role of concurrent treatment with PPS and insulin-like growth factor - 1 (IGF-1) as a prophylactic therapy for retardation of protease- tissue inhibitor of metalloproteases. It has also been shown that NaPPS inhibits human lysosomal elastase, a serine proteinase [Baici *et al.*, 1981].

Figure 2: Disease modifying properties of PPS (* sites of PPS action)

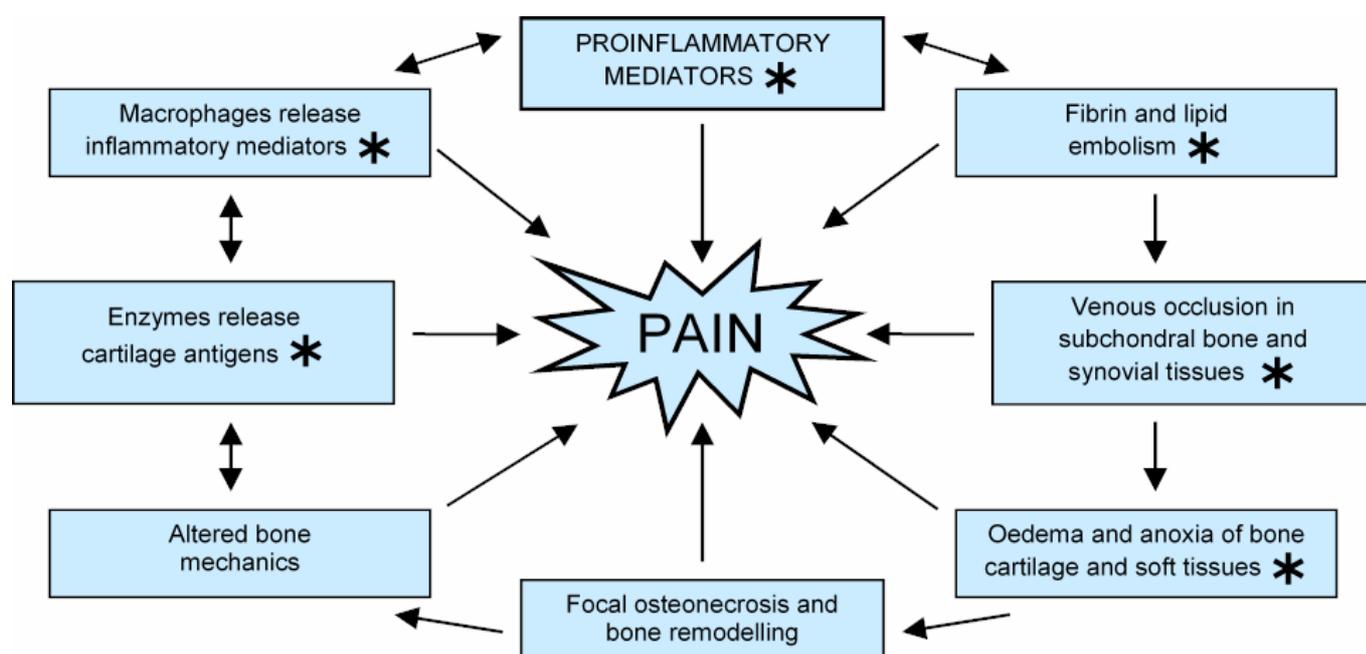


Pain in OA is the most important clinical sign in humans [Moskowitz, 1984] and domestic animals [Caron, 1996; Innes, 1995; Johnston, 1997; Hulse, 1998; McLaughlin, 2000]. Pain is the principle cause of reduced performance and its pathogenesis is usually multifactorial, however, many aspects of the reaction of the nervous system to noxious stimuli (nociception) and the sensory and emotional experience associated with a noxious stimulus (pain) remain unclear [Caron, 1996; Johnston 1997]. The sites where PPS acts on pain in OA are summarised in Figure 3.

The peripheral neuroanatomy of joints is reported to be similar in many species [Caron, 1996] and the popular classification of articular nerve endings in mammalian appendicular joints as four receptor types - types 1, 2, 3 and 4 is universally accepted. Type 1 mechanoreceptors are located in the superficial areas of the joint capsule and are low-threshold receptors. That is, they are stimulated by relatively mild mechanical stimuli and remain active while a mechanical stimuli persists. Type 2 receptors are found more deeply in the joint capsule and are low-threshold,

rapidly adapting mechanoreceptors. They are inactive when joints are immobile and become activated when joints undergo movement or experience tension. Type 3 receptors are large and are restricted to intra-articular and periarticular ligaments near their insertions. They are high-threshold slowly adapting mechanoreceptors that are inactive in stationary joints and with active and passive movement over a limited range and become activated only when joint excursions occur near physiological limits or when ligaments containing them undergo powerful traction forces. Type 3 receptors are also capable of nociception and modifying type 1 and 2 receptor-mediated reflexes. Type 4 'receptors' are free nerve endings rather than specific end organs like receptors 1 to 3 of which there are two types - type 4a and 4b. Type 4 endings are high threshold, slowly adapting nociceptors and their activation signals impending or actual tissue damage. Type 4 endings are polymodal and respond to mechanical, heat and chemical stimuli such as lactic acid, kinins, serotonin, histamine and prostaglandin E₂.

Figure 3: Biochemical origins of pain in OA and sites (*) where PPS intervenes

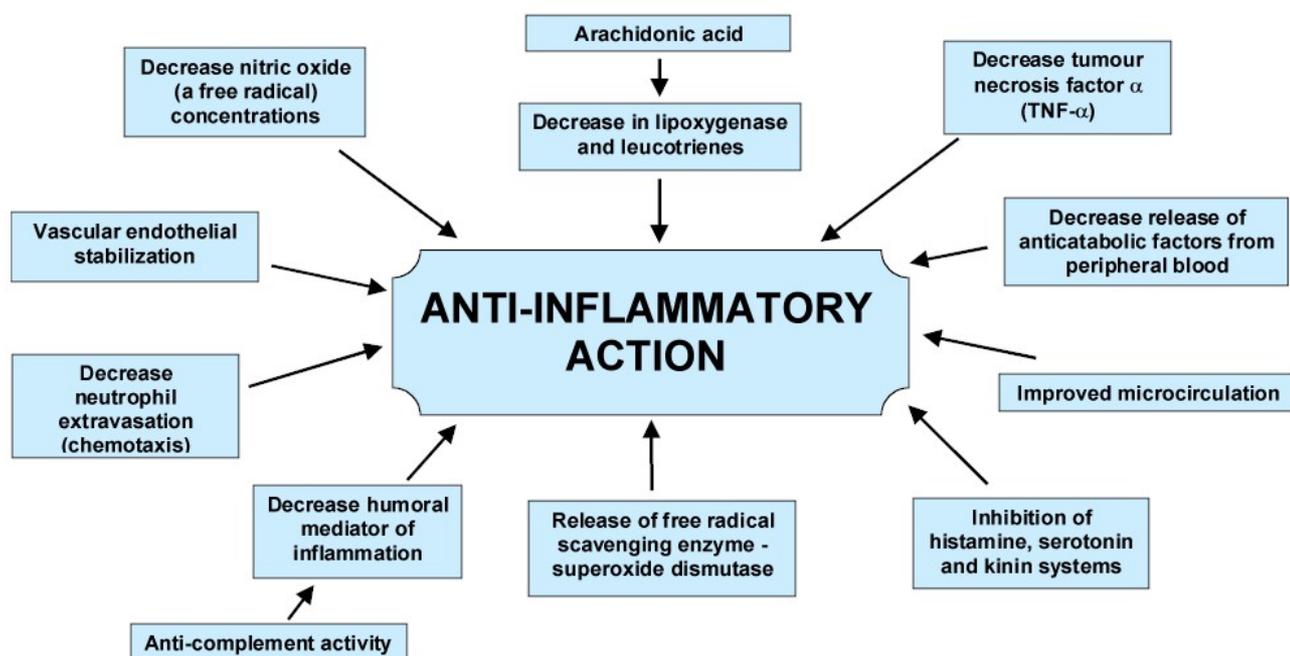


The potent anti-inflammatory and anti-complement activities of PPS have been consistently demonstrated in different models of severe inflammation. Kalbhen and co-workers [Kalbhen 1971, 1972, 1973; Kalbhen *et al.*, 1978] using oedemas induced in rat paws by injection of dextran, formaldehyde, trypsin, hyaluronidase, carrageenan or kaolin. For all of these experimentally induced oedemas, a dose-response correlation was observed using NaPPS within the concentration range of 25 - 100 mg/kg when the drug was administered subcutaneously. It was concluded by Kalbhen (1973, 1978) that unlike sodium salicylate, phenylbutazone or indomethacin, NaPPS was effective against all the types of inflammogens his group had examined. The mechanism of action in this regard was attributed largely to stabilisation of the peripheral vascular system and improvement of the microcirculation in the inflamed tissues.

According to Walb, Loos and Hadding (1971), NaPPS possesses marked anti-complementary activities. Using sensitised erythrocytes *in vitro*, it was found that NaPPS was ten times more potent than heparin in preventing the lysis by a complement preparation when used over the concentration range 5.0 - 8.3 µg/mL. *In vitro* NaPPS also inhibited the complement C1-esterase, the ED50 lying in the range of 7 - 8 µg/mL. In a series of consecutive papers, Berthoux and co-workers (1977a,b) confirmed the anti-complementary activity of NaPPS both *in vitro* and *in vivo*. From these studies it was concluded that the *in vivo* anti-complement activity of NaPPS were sufficiently strong to suggest that a decrease liberation of humoral mediators of inflammation would occur during its clinical usage.

The anti-inflammatory action of PPS is mediated through several pathways the most important being summarised in Figure 4.

Figure 4: Anti-inflammatory action of PPS



MATERIALS AND METHODS

Study design and recruitment of dogs

The study was a multi-centre, double-blind, comparator controlled, randomised study. The objective of the study was to establish the efficacy and safety of 3mg/kg NaPPS marketed at *CARTROPHEN VET*[®] for the treatment of OA. Animals (dogs) were drawn from the existing client base of ten private practices in Germany. Dogs of any age, breed, sex and duration or severity of OA were accepted into the study. Following screening and informed consent, animals were randomly assigned to treatments using a randomisation schedule prepared by the Sponsor. Veterinarian and owners remained blinded to treatments throughout the study period with all medications supplied in blinded packages. Dogs assigned to the control group were administered 4mg/kg carprofen (*Rimadyl*[®], *Zenecarp*) for 28 consecutive days and placebo injection at 7 day intervals on four occasions. Dogs assigned to the treatment group received 3mg/kg NaPPS (*CARTROPHEN VET*[®]) by subcutaneous injection at 7 day intervals on four occasions and placebo capsules for 28 consecutive days.

Diagnosis of OA was based on radiographic examination and the presence of the clinical signs of OA according to conventional criteria, namely lameness, pain on palpation, stiffness and a decrease in activity. Cases had a specific diagnosis based on history, full physical examination and radiographic examination (2 views). Radiographs had to demonstrate some evidence of OA. Changes consistent with a diagnosis of OA include osteophyte formation, synovial effusion, subchondral sclerosis, decreased joint space and soft tissue swelling.

Re-examination protocol

Dogs were assessed by the veterinarian at weekly intervals during treatment (Weeks 1 to 4) and four weeks after treatment had ceased (Week 8). The same veterinarian for each individual dog undertook the physical examination at each visit.

The primary outcomes measured were improvement at Week 4 and Week 8 from baseline for lameness (scored on a five point scale from 0=no lameness to 4=won't use), pain on manipulation (scored on a five point Likert scale from 1=no pain to 5=screams with pain) and orthopaedic score (sum of pain and lameness scores) and the investigator's overall impression at Week 8. In addition the secondary outcomes of improvement at Week 4 and Week 8 from baseline for gait ataxia, gait weakness, gait stiffness, coat condition, condition of dog, body weight

and "get-up-and-go" were measured. Safety was measured by recording the frequency and severity of any suspect adverse reactions.

Measurements of outcome and data analysis

Data analysis was designed to establish if carprofen and NaPPS were effective treatments for OA and to determine if there were any differences between the efficacy of the treatments.

The Stratified Wilcoxon rank-sum test [Bajorski and Petkau, 1999] was used to determine differences between treatments in improving lameness, pain, orthopaedic score, gait ataxia, gait weakness, gait stiffness and get up and go. This method was the definitive test for drawing inferences and conclusions in the study. The strata used were the baseline values and the statistics over all the strata for each week were pooled. Analysis of Veterinary Impression was undertaken using the continuation-ratio model.

The Continuation-odds ratio approach was used to determine differences between treatments in improving lameness, pain, orthopaedic score, veterinary impression, gait ataxia, gait weakness, gait stiffness, get up and go and second joint parameters (lameness, pain and orthopaedic score). Analysis performed by this method was secondary to the Stratified Wilcoxon rank sum test.

The secondary parameters of dog condition, coat condition and body weight were assessed by Stratified Longitudinal Multiple Rank Regression. The distribution of responses for these three parameters defied formal tests for normality and therefore the Stratified Wilcoxon rank-sum test could not be used. This method was the definitive test for drawing conclusions about dog condition, coat condition and body weight.

The activity of each treatment was determined using the Wilcoxon signed rank test for both primary and secondary outcomes.

Fishers exact test was used to determine if there was a statistical difference between treatments in the number of adverse events reported.

The level of significance for all statistical methods was $p < 0.05$.

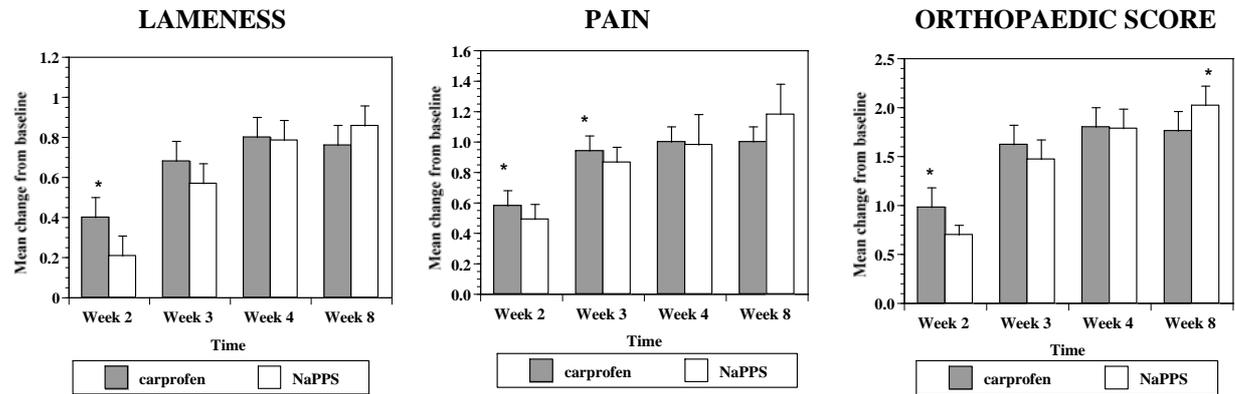
In addition the effectiveness of both carprofen and *CARTROPHEN VET*[®] treatments in reducing severe lameness, pain and orthopaedic score was assessed by graphing the mean change from baseline (Week 1) in these parameters. Severe lameness corresponded to the clinical signs "won't use" or "just puts affected limb on ground", severe pain was defined as the dog "vocalising" or "wincing and withdrawing" upon manipulation of the affected limb and severe orthopaedic score was considered to be a score of 6, 7, 8 or 9.

RESULTS

One hundred and four dogs were enrolled in the study (51 control and 53 *CARTROPHEN VET*[®]). A total of 33 different breeds participated in the study. The greatest number of animals treated fell in the age range 6.1 to 9.0 years in the carprofen treatment group (16) and in the 3.1 to 6.0 year old age group for treated animals (18). The average age was 8.2 years in the carprofen treatment group compared to 6.9 years in the NaPPS treatment group. Twenty two males and 29 females received carprofen treatment compared to 31 males and 22 females receiving NaPPS treatment.

Analysis of the primary outcomes of lameness, pain and orthopaedic score, revealed that there was statistically significant improvement following treatment with NaPPS compared to treatment with carprofen at Week 8 (four weeks after treatment had ceased) in orthopaedic score ($p = 0.013$). Improvement following carprofen treatment relative to NaPPS treatment was statistically significant for lameness at Week 2 ($p < 0.001$), pain at Week 2 ($p = 0.023$) and Week 3 ($p < 0.001$) and orthopaedic score at Week 2 ($p = 0.041$). The statistically significant difference at Week 2 for lameness in favour of carprofen was diminished by Week 8 with NaPPS the more favourable treatment ($p = 0.129$). A summary of the efficacy results for these primary outcomes is presented in Figure 5.

Figure 5: Mean change from baseline during treatment (Weeks 2, 3 and 4) and 4 weeks after treatment ceased (Week 8) for the primary outcomes of lameness, pain and orthopaedic score (*=significant at $p < 0.05$)

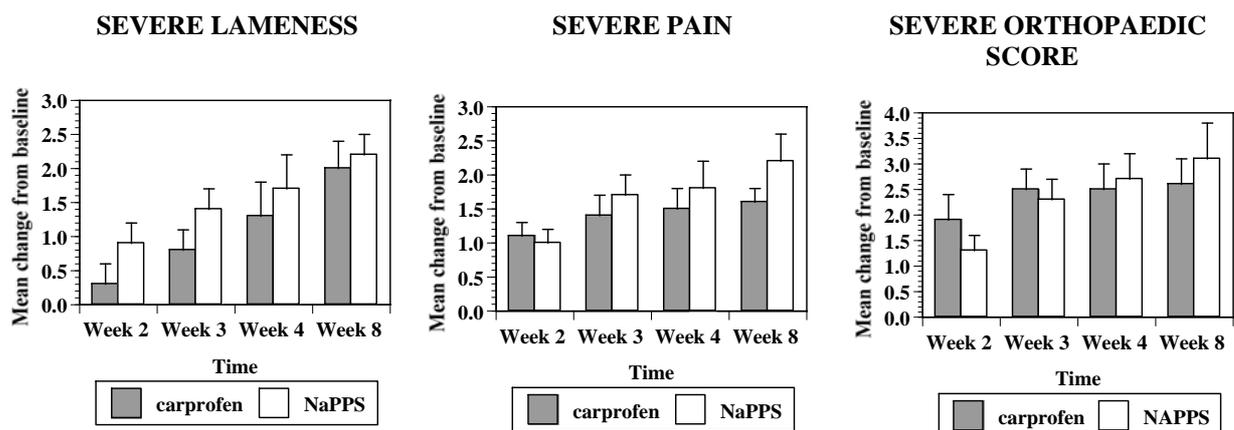


According to the primary outcome veterinarians' impression of the overall response to treatment, both NaPPS and carprofen treatments were highly effective and there was no statistically significant difference between the two drugs ($p=0.909$). There was however, a slight advantage in favour of NaPPS in the estimate of the magnitude of the effect.

Analysis of the activity of each treatment compared to the corresponding baseline value demonstrated that both NaPPS and carprofen were very effective treatments with statistically significant improvements in all primary outcome parameters (lameness, pain and orthopaedic score) at all weeks ($p < 0.05$). The efficacy of each treatment was also demonstrated for secondary outcomes with significant improvements in gait stiffness and get up and go at all weeks and gait ataxia and gait weakness at Weeks 3, 4 and 8 ($p < 0.05$). No statistically significant change to dog condition, coat condition or body weight was noted at any week for either treatment ($p > 0.05$).

In order to assess the effectiveness of each drug in cases of severe OA, animals presenting with severe lameness, severe pain and severe orthopaedic score were analysed for the mean change from baseline (Week 1). Although numbers in each group were small, the results demonstrated that both NaPPS and carprofen were effective treatments for animals suffering severe OA. Figure 6 summarises the mean change from baseline in lameness, pain and orthopaedic score in animals with severe OA.

Figure 6: Mean change from baseline in lameness, pain and orthopaedic score for animals suffering severe OA



Six adverse events were reported during the study - four in the NaPPS group and two in the carprofen group. None of the four adverse events in the NaPPS group were considered to be associated with the treatment, while both of the adverse events reported in the carprofen group were considered to be possibly associated with the treatment. The incidence of 2/51 carprofen and 4/53 NaPPS adverse events is not statistically significant ($p = 0.687$).

CONCLUSION

NaPPS a disease modifying anti-osteoarthritic drug with anti-inflammatory activities is as effective as the NSAID and analgesic drug, carprofen, in the treatment of lameness and pain of OA at the end of the 4 week treatment period. NaPPS maintained its effectiveness longer than carprofen, as indicated by the significant improvement following NaPPS treatment compared to carprofen treatment in orthopaedic score at Week 8 ($p=0.013$). In addition NaPPS and carprofen were both found to be effective in treating the severe clinical signs of OA with some evidence that NaPPS treatment is superior.

REFERENCES

- Adams M (1994) Changes in aggrecan populations in experimental osteoarthritis. *Osteoarthritis Cart* 2:155-164
- Alexander JW (1979) Osteoarthritis (Degenerative Joint Disease) in the dog. *Canine Practice* 6(1):31-34
- Altman RD (1991) Classification of disease: Osteoarthritis. *Semin Arthritis Rheum* 20 (6) Supp 2:40-47
- Altman RD, Tennenbaum J, Latta L, Riskin W, Blanco LN, Howell DS (1984) Biomechanical and biochemical properties of dog cartilage in experimentally induced osteoarthritis. *Ann Rheum Dis* 43:83-90
- Baici A, Salgam P, Fehr K, Böni (1981) A. Inhibition of human elastase from polymorphonuclear leucocytes by gold sodium thiomalate and pentosan polysulfate (SP-54[®]). *Biochem Pharmacol* 30:703-708.
- Bajorski, P and Petkau, J (1999). Nonparametric Two-Sample Comparisons of Changes on Ordinal Responses, *J.Am.Stat.Assoc.*, 94, 970-978
- Berthoux FC, Freyria A-J, Traeger J (1977b) Anticomplementary activity of a polyanion, pentosan poly-sulfoester. III - Mechanism of functional inactivation of the different properdin and complement system molecules. *Path Biol* 25(3):179-184
- Berthoux FC, Freyria A-M, Traeger J (1977a) Anticomplementary activity of a polyanion: Pentosan poly sulfoester. II. Mode of action and *in vitro* inhibition of human complement hemolytic activity. *Pathol Biol* 25(2):105-108
- Brandt KD, Braunstein EM, Visco DM, O'Connor B, Heck D, Albrecht M (1991a) Anterior (cranial) cruciate ligament transection in the dog - A bona-fide model of osteoarthritis, not merely of cartilage injury and repair. *J Rheumatol* 18(3):436-446
- Brandt KD, Myers SL, Burr D, Albrecht M (1991b) Osteoarthritic changes in canine articular cartilage, subchondral bone, and synovium fifty-four months after transection of the anterior cruciate ligament. *Arthritis Rheum* 34(12):1560-1570
- Brandt KD, Slowman-Kovacs S. (1986) Nonsteroidal antiinflammatory drugs in treatment of osteoarthritis. *Clin Orthop* 213:84-91.
- Carney SL, Billingham MEJ, Caterson B, Ratcliffe A, Bayliss MT, Hardingham TE, Muir H (1992) Changes in proteoglycan turnover in experimental canine osteoarthritic cartilage. *Matrix* 12(2):137-147
- Carney SL, Billingham MEJ, Muir H, Sandy JD (1985) Structure of newly synthesised [35S]-proteoglycans and [35S]-proteoglycan turnover products of cartilage explant cultures from dogs with experimental osteoarthritis. *J Orthop Res* 3(2): 140-147
- Caron JP. (1996) Neurogenic factors in joint pain and disease pathogenesis. In "Joint Disease of the Horse", editors CW. McIlwraith and GW. Trotter, WB. WB Saunders Company, Philadelphia, pp. 70-80.
- Cox JS, Nye CE, Schaeffer WW, Woodstein IJ (1975) The degenerative effects of partial and total resection of the medial meniscus in dogs' knees. *Clin Orthop* 109:178-183
- Dourado GS, Adams ME, Matyas JR, Huang D (1996) Expression of biglycan, decorin and fibromodulin in the hypertrophic phase of experimental osteoarthritis. *Osteoarthritis Cart* 4(3):187-196
- Dunham J, Shackleton DR, Nahir AM, Billingham MEJ, Bitensky L, Chayen J, Muir IH (1985) Altered orientation of glycosaminoglycans and cellular changes in the tibial cartilage in the first two weeks of experimental canine osteoarthritis. *J Orthop Res* 3:258-268
- Elkins AD, Pechman R, Kearney MT, Herron M (1991) A retrospective study evaluating the degree of degenerative joint disease in the stifle joint of dogs following surgical repair of anterior cruciate ligament rupture. *J Am Anim Hosp Assoc* 27:533-540

- Engelhardt G. (1996) Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. *Br J Rheumatol* 35:4-12.
- Engelhardt G, Homma D, Schlegel K, Utzmann R, Schnitzler C. (1995) Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. *Inflamm Res* 44:423-433.
- Felson DT. (1988) Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev* 10:1-28.
- Fife RS (1986) Alterations in a cartilage matrix glycoprotein in canine osteo-arthritis. *Arthritis Rheum* 29(12):1493-1500
- Fox SM, Johnston SA (1997) Use of carprofen for the treatment of pain and inflammation in dogs. *J Am Vet Med Assoc* 210(10):1493-1498
- Gabriel SE, Wagner JL. (1997) Costs and effectiveness of nonsteroidal anti-inflammatory drugs. The importance of reducing side effects. *Arthritis Care Research* 10:56-63.
- Gardner DL (1983) The nature and causes of osteoarthrosis. *Br Med J* 286:418-424
- Ghosh P (1991) Osteoarthritis: aetiopathogenesis and management. *Modern Med Aust* :68-80
- Ghosh P. (1999) The pathobiology of osteoarthritis and the rationale for the use of pentosan polysulfate for its treatment. *Seminars in Arthritis and Rheumatism* 28(4):211-267.
- Ghosh P, Sutherland JM, Taylor TKF, Bellenger CR, Pettit GD (1984) The effect of bilateral medial meniscectomy on articular cartilage of the hip joint. *J Rheumatol* 11:197-201
- Ghosh P, Sutherland JM, Taylor TKF, Pettit GD, Bellenger CR (1983a) The effects of postoperative joint immobilization of articular cartilage degeneration following meniscectomy. *J Surg Res* 35:461-473
- Ghosh P, Taylor TKF, Pettit GD, Horsburgh BA, Bellenger CR (1983b) Effect of postoperative immobilisation on the regrowth of the knee joint semilunar cartilage: an experimental study. *J Orthop Res* 1:153-164
- Grumbles RM, Howell DS, Howard GA, Roos BA, Setton LA, Mow VC, Ratcliffe A, Muller FJ, Altman RD (1995) Cartilage metalloproteases in disuse atrophy. *J Rheumatol* 22(Suppl. 43):146-148
- Guilak F, Ratcliffe A, Lane N, Rosenwasser MP, Mow VC (1994) Mechanical and biochemical changes in the superficial zone of articular cartilage in canine experimental osteoarthritis. *J Orthop Res* 12(4):474-484
- Hamerman D (1993) Aging and osteoarthritis: Basic mechanisms. *J Am Geriatr Soc* 41(7):760-770
- Hannan N, Ghosh P, Bellenger C, Taylor T (1987) The systemic administration of glycosaminoglycan polysulphate (Arteparon) provides partial protection of articular cartilage from damage produced by meniscectomy in the canine. *J Orthop Res* 5:47-59
- Hulse D. (1998) Treatment methods for pain in the osteoarthritic patient. *Veterinary Clinics of North America: Small Animal Practice* 28(2): 361-375
- Innes, J. (1995) Diagnosis and treatment of osteoarthritis in dogs. *In Practice* 17, 102-109
- Isaacs JP (1996) Adverse effects of non-steroidal anti-inflammatory drugs in the dog and cat. *Aust Vet Practit* 26(4):180-186
- Johnson RG, Poole AR (1990) The early response of articular cartilage to ACL transection in a canine model. *Exp Pathol* 38(1):37-52
- Johnston, S.A. (1997) Osteoarthritis: Joint anatomy, physiology and pathobiology. *Veterinary Clinics of North America: Small Animal Practice* 27:699-723

- Johnston SA, Budsberg SC (1997) Nonsteroidal antiinflammatory drugs and corticosteroids for the management of canine osteoarthritis. *Vet Clin Sm* 27(4):841-862
- Jones, Jr JP. (1993) Fat embolism, intravascular coagulation and osteonecrosis. *Clin Orthop Rel Res* 292:294-308
- Kalbhen DA (1972) Entzündungshemmung durch Pentosanpolysulfat. *Dtsch med Wschr* 97:1-3
- Kalbhen DA (1973) Pharmacological studies on the anti-inflammatory effect of a semi-synthetic polysaccharide (pentosan polysulfate). *Pharmacology* 9:74-79
- Kalbhen DA (1978) The biochemical and pharmacological basis of the antiphlogistic/antirheumatic effect of pentosan polysulphate. *Wein Klin Wochenschrift* 90(3):101-105
- Kalbhen DA, Van Heek HJ (1971) Zur antiphlogistischen Wirkung von Pentosanpolysulfat auf das experimentelle Pfotenödem der Ratte. *Arzneim-For* 21:1608-1612
- Kealy RD, Lawler DF, Ballam JM, Lust G, Smith GK, Biery DN, Olsson SE (1997) Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. *J Am Vet Med* 210(2):222-225
- Lichtenstein DR, Syngal S, Wolfe MM. (1995) Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. The double-edged sword. *Arthritis Rheum* 38:5-18.
- Lust G, Summers BA (1981) Early, asymptomatic stage of degenerative joint disease in canine hip joints. *Am J Vet Res* 42:1849-1855
- MacPhail CM, Lappin MR, Meyer DJ, Smith SG, Webster CR, Armstrong PJ (1998) Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *JAVMA* 212(12):1895-1901.
- Mankin HJ, Brandt KD, Shulman LE (1986) Workshop on etiopathogenesis of osteoarthritis proceedings and recommendations. *J Rheumatol* 13(6):1126-1160
- Manoukian AV, Carson JL. (1996) Nonsteroidal anti-inflammatory drug-induced hepatic disorders. Incidence and prevention. *Drug Safety* 15:64-71.
- March L, Brooks P (1996) Osteoarthritis: the disease of the third millennium. *Modern Medicine of Australia* June:18-29
- McDevitt CA, Muir H (1976) Biochemical changes in the cartilage of the knee in experimental and natural osteoarthritis in the dog. *J Bone Joint Surg* 58-B:94-101
- McDevitt CA, Muir H, Pond MJ (1974) Canine Articular Cartilage in Natural and Experimentally Induced Osteoarthrosis. *Biochemical Society Transactions* 1:287-289
- McKenzie LS, Horsburgh BA, Ghosh P, Taylor TKF (1976) Effect of anti-inflammatory drugs on sulphated glycosaminoglycan synthesis in aged human articular cartilage. *Ann Rheum Dis* 35:487-497
- McLaughlin (2000) Management of chronic osteoarthritic pain. *Veterinary Clinics of North America: Small Animal Practice* 30, 933-949
- Moskowitz RW. (1984) Osteoarthritis - symptoms and signs. In "Osteoarthritis - Diagnosis and Management", editors Moskowitz RW., Howell DS., Goldberg VM. and Mankin HJ. WB. Saunders Company, Philadelphia, pp. 149-154.
- Myers SL, Brandt KD, O'Connor BL, Visco DM, Albrecht ME (1990) Synovitis and osteoarthritic changes in canine articular cartilage after anterior cruciate ligament transection - effect of surgical hemostasis. *Arthritis Rheum* 33(9):1406-1415

- Noble S, Balfour JA. (1996) Meloxicam. *Drugs* 51:424-443.
- Palmoski MJ, Brandt KD (1980) Effects of some nonsteroidal antiinflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. *Arthritis Rheum* 23:1010-1020
- Pedersen NC, Pool RR, Morgan JP (1983) Joint diseases of dogs and cats in *Textbook of veterinary internal medicine: diseases of the dog and cat second WB Saunders Company* 2187-2235
- Pelletier J-P, Martel-Pelletier J, Ghandur-Mnaymneh L, Howell DA, Woessner (Jr) JF (1985) Role of synovial membrane inflammation in cartilage collagen matrix breakdown in the Pond-Nuki dog model of osteoarthritis. *Arthritis Rheum* 28:554-561
- Perazella MA and Tray K, (2001) Selective cyclooxygenase-2 inhibitors: A pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *The American Journal of Medicine* 111: 64-67
- Pritzker KP (1994) Animal models for osteoarthritis: Processes, problems and prospects. *Ann Rheum Dis* 53(6):406-420
- Ratcliffe A, Shurety W, Caterson B (1993) The quantitation of a native chondroitin sulfate epitope in synovial fluid lavages and articular cartilage from canine experimental osteoarthritis and disuse atrophy. *Arthritis Rheum* 36(4):543-551
- Rogachefsky RA, Dean DD, Howell DS, Altman RD (1993) Treatment of canine osteoarthritis with insulin-like growth factor-1 (IGF-1) and sodium pentosan polysulfate. *Osteoarthritis Cart* 1:105-114
- Sandy J, Adams M, Billingham M, Plaas A, Muir H (1984) *In vivo* and *in vitro* stimulation of chondrocyte biosynthetic activity in early experimental osteoarthritis. *Arthritis Rheum* 27:388-397
- Smith MM and Ghosh P. (2001) Experimental models of osteoarthritis. In *Osteoarthritis - Diagnosis and Medical/Surgical Management*, Moskowitz RW, Howell DS, Altman RD, Buckwalter JA and Goldberg VM. W.B. Saunders Company, New York, 171-199
- Van Pelt RW (1965) Comparative Arthrology in Man and Domestic Animals. *JAVMA* 147(9):958-967
- Vane JR, Botting RM. (1996) Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 25:9-21.
- Vasseur PB, Berry CR (1992) Progression of stifle osteoarthrosis following reconstruction of the cranial cruciate ligament in 21 dogs. *J Am Anim Hosp Assoc* 28(2):129-136
- Venn G, Billingham MEJ, Hardingham TE (1995) Increased proteoglycan synthesis in cartilage in experimental canine osteoarthritis does not reflect a permanent change in chondrocyte phenotype. *Arthritis Rheum* 38(4):525-531
- Venn G, Nietfeld JJ, Duits AJ, Brennan FM, Arner E, Covington M, et al. (1993) Elevated synovial fluid levels of interleukin-6 and tumor necrosis factor associated with early experimental canine osteoarthritis. *Arthritis Rheum* 36:819-826.
- Walb D, Loos M, Hadding U (1971) Antikomplementare Wirkung eines semisynthetischen Pentosan-Polysulfato-Esters In-vitro-Untersuchungen über Angriffspunkt und Wirkungsunterschiede zum Heparin. *Zschr Naturforsch* 26:403-408