Efficacy and safety of glycosylated undenatured type-II collagen (UC-II) in therapy of arthritic dogs[§]

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DeParle L. A., Gupta R. C., Canerdy T. D., Goad J. T., D'Altilio M., Bagchi M., Bagchi D. Efficacy and safety of glycosylated undenatured type-II collagen (UC-II) in therapy of arthritic dogs. *J. vet. Pharmacol. Therap.* **28**, 385–390.

In large breed dogs, arthritis is very common because of obesity, injury, aging, immune disorder, or genetic predispositions. This study was therefore undertaken to evaluate clinical efficacy and safety of undenatured type-II collagen (UC-II) in obese-arthritic dogs. Fifteen dogs in three groups received either no UC-II (Group I) or UC-II with 1 mg/day (Group II) or 10 mg/day (Group III) for 90 days. Lameness and pain were measured on a weekly basis for 120 days (90 days treatment plus 30 days post-treatment). Blood samples were assayed for creatinine and blood urea nitrogen (markers of renal injury); and alanine aminotransferase and aspartate aminotransferase (evidence of hepatic injury). Dogs receiving 1 mg or 10 mg UC-II/day for 90 days showed significant declines in overall pain and pain during limb manipulation and lameness after physical exertion, with 10 mg showed greater improvement. At either dose of UC-II, no adverse effects were noted and no significant changes were noted in serum chemistry, suggesting that UC-II was well tolerated. In addition, dogs receiving UC-II for 90 days showed increased physical activity level. Following UC-II withdrawal for a period of 30 days, all dogs experienced a relapse of overall pain, exercise-associated lameness, and pain upon limb manipulation. These results suggest that daily treatment of arthritic dogs with UC-II ameliorates signs and symptoms of arthritis, and UC-II is well tolerated as no adverse effects were noted.

(Paper received 25 January 2005; accepted for publication 18 April 2005)

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INTRODUCTION

Approximately 43 million Americans or 16% of the US population suffer from arthritis. The two most common types of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA) (CDC, 1994; Helmick *et al.*, 1995). OA is an inflammatory joint disease, which is characterized by degeneration of the cartilage, hypertrophy of bone at the margins and changes in the synovial membrane. The disease is accompanied by pain and stiffness, particularly after prolonged activity. RA is a chronic disease that is characterized by inflammation, pain, swelling and stiffness of multiple joints in both humans and dogs. Painful arthritis can result from degeneration of the cartilage or inflammation of the soft connective tissue. In the case of RA, the body's immune system misidentifies collagen as a foreign substance and sends antibodies to attack and destroy it. Chronic joint inflammation usually results in progressive joint destruction, deformity and loss of function (van Roon *et al.*, 2001). Arthritis is one of the most commonly diagnosed canine diseases in most large breeds. Dogs often become arthritic due to injury, obesity, aging, or immune disorder. Some breeds of dogs are even genetically predisposed to develop arthritis (Hielm-Bjorkman *et al.*, 2003).

In the recent past, the treatment options for arthritis were typically nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination with what are known as disease-modifying anti-rheumatic drugs. Present treatment tries to alleviate pain, control inflammation, and preserve ability to perform daily

[§]Presented at the 10th International Congress of Toxicology, Tampere, Finland, July 10–15, 2004; 45th Annual Meeting of the American College of Nutrition, Long Beach, CA, September 30–October 3, 2004; and 44th Annual Meeting of Society of Toxicology, New Orleans, March 6–10, 2005. Part of the Master's thesis (L. A. DeParle), Murray State University, Murray, KY, USA.

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functions. However, rheumatoid arthritis is poorly responsive to current therapy. NSAIDs (COX enzymes inhibitors) eliminate pain but do not eliminate signs and symptoms of active disease. As is well known, chronic use of NSAIDs is linked to numerous side effects, including gastrointestinal (GI) bleeding and renal dysfunction (PDR, 1998; Muhlfeld & Floege, 2005). Anti-inflammatory drugs such as aspirin and ibuprofen are non-specific inhibitors of COX enzymes (both COX-1 and COX-II). They inhibit the production of inflammatory prostaglandins, resulting in their therapeutic effect, but also inhibit the production of constitutive prostaglandins, resulting in side effects, such as GI bleeding (Matteson, 2000). COX-II inhibitors include Vioxx (rofecoxib) and Celebrex (celecoxib), which are considered safer than nonspecific COX inhibitors. Most recently, Vioxx has been removed from the market, because it increases the risks for heart attack and stroke, and Celebrex too exhibits side effects such as allergy, GI irritation and bleeding, and fluid retention (Infante & Lahita, 2000; Schuna & Megeff, 2000; Matheson & Figgilt, 2001). Therefore, a safe therapy for arthritis is needed. Glycosylated undenatured Type-II collagen (UC-II) is derived from chicken sternum and prepared under good manufacturing practices (GMPs), using low temperature, which preserves its undenatured form and ensures biological activity.

In the present investigation, the undenatured form was used, since this form of UC-II is found to be significantly more effective than denatured against arthritis. Figure 1 presents the electron microscopic photographs of undenatured and denatured UC-II collagen. Time–dose studies have revealed that once UC-II is ingested, stomach acids and enzymes perform a partial digestion of the collagen matrix, resulting in chains of soluble collagen molecules of varying length, containing biologically active epitopes. These structurally precise natural epitopes in UC-II interact with Peyer's Patches and trigger the complex series of immunological events that, in the case of rheumatoid arthritis, down-regulates the body's out-of-control autoimmune response. In the case of osteoarthritis, UC-II can promote a reduction in inflammation. In earlier studies, UC-II was found to be effective in ameliorating pain associated with rheumatoid arthritis in humans (Trentham *et al.*, 1993). In a small pilot study, UC-II was also found to be effective in relieving pain associated with osteoarthritis (Bagchi *et al.*, 2002).

UC-II reacts with the body's immune system to improve crippling signs and symptoms of arthritis. Type-II collagen is the principle structural protein found in cartilage and is responsible for its tensile strength and toughness (Bagchi *et al.*, 2002). Type-II collagen is one of the primary connective tissues of the body, providing flexibility and support to bone joints. UC-II functions through a process called oral tolerization. This process takes place in the small intestine where food is absorbed. Through a complex series of immunological events, patches of lymphoid tissue (Peyer's Patches) surrounding the small intestine, screens incoming compounds and serve as a 'switch' to turn the body's immune response to foreign substances on or off, depending upon what the substance is. A small amount of undenatured type-II collagen (10 mg) taken orally has been shown to turn off the immune response targeted at type-II collagen in joint cartilage, and adverse effects have not been noted. The process helps the body to differentiate between elements that are foreign invaders to the body and those that are nutrients and are good for the body (Weiner, 1997; Trentham, 1998). In order to be effective, it is recommended that the product be given orally, as it is absorbed in the small intestine. Type-II collagen, when taken orally, has the ability to stop the immune system from attacking and damaging its own joint cartilage, thereby improving joint mobility and flexibility (Trentham, 1998; Trentham *et al.*, 1993, 2001). Several other human studies have confirmed that undenatured type-II collagen reacts with the immune system to promote healthy joints and improve mobility and flexibility. One study has demonstrated that regular small doses of Type-II undenatured collagen, at an oral dose of 10 mg/day for 42 days in five-female subjects, improved joint mobility and flexibility, thereby reducing significant pain and morning stiffness. No adverse effects were noted in patients receiving UC-II (Bagchi *et al.*, 2002). However, most over-the-counter drugs administered to arthritic dogs may cause gastrointestinal and cardiovascular complications, in addition to other side effects

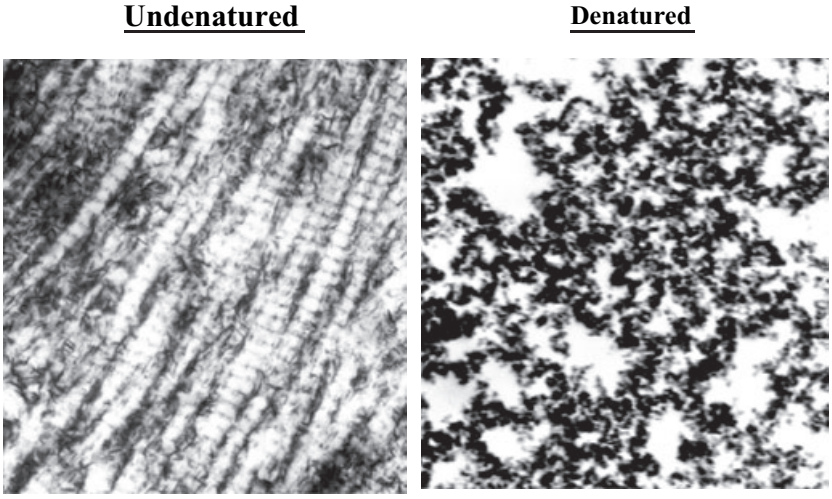

Fig. 1. Electron microscopy photographs of undenatured type-II collagen (UC-II) collagen (Courtesy, Bagchi *et al.*, 2002).

associated with hepatic and renal damage (Lamarque, 2004; Solomon *et al.*, 2004). The present investigation was undertaken with the specific objective to determine whether UC-II can ameliorate arthritic symptoms in dogs (regardless of etiology), following supplementation at 1 mg/day or 10 mg/day for 90 days, with minimal or no side effects.

MATERIALS AND METHODS

Animals

A group of 15 adult-household dogs, weighing between 44 and 103 pounds, was selected for this study based on the signs of arthritis, such as joint stiffness, lameness, and pain. These dogs had swollen joints, and were experiencing difficulty in getting up or down and walking. Arthritic dogs having any other serious disease (such as hepatic or renal) or complication (tumor, etc.) were excluded from the study. Throughout the study, dogs remained with their owners, and therefore institutional animal care and use committee (IACUC) approval was not required. The owner consent was obtained before initiation of any experiment.

Supplement

Type-II glycosylated undenatured chicken sternum cartilage (UC-II) in capsule form (1 mg or 10 mg dosages) used in this study was provided by InterHealth Nutraceuticals Inc. (Benicia, CA, USA).

Experimental design

Dogs were randomly divided into three groups. Group 1, the control group, did not receive UC-II. Dogs in Groups 2 and 3 were administered UC-II, 1 and 10 mg/day, respectively, for 90 days, followed by a 30-day-withdrawal period. None of the dogs received any NSAIDs before or during the study period. Dog owners were blinded for UC-II treatment.

Blood collection and biochemical assays

Blood was collected by jugular venipuncture using a 22-gauge needle and 12 cm^3 syringes. Serum was separated in a marble top tube (serum separating tubes without anticoagulant) and transferred into plastic snap-top tubes. Samples were frozen immediately and kept at −80 °C until analysis for blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), using Beckman Coulter CX5-PRO Synchron Clinical System (Fullerton, CA).

Gross observations

Gross observations were recorded on a weekly basis for a period of 120 days using a questionnaire evaluation based on daily activities. Results were also obtained by physical evaluation during monthly exams. Overall pain was measured as a general gross observation, which included trouble in standing after sitting, or trouble in sitting after standing, vocalization, crying, etc. (results were graded on a scale of 0–10: 0, no pain, 5, moderate; and 10, severe and constant pain). Pain during limb manipulation was evaluated by animals' vocalization or other observations of pain during the extension and flexion of all four limbs for few min (results were graded on a scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; 4, severe and constant). Lameness was measured after physical exercise for gross observations, which included limping, holding limb up, rigidity of limbs, etc. Signs of pain and lameness were noted on a scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; 4, severe and constant.

Statistical analysis

The data of pain presented in Fig. 2 and of serum chemistry presented in Table 1 are means ± SEM ($n = 4$–5 dogs in each group). Statistical significance of difference was determined by analysis of variance (ANOVA) coupled with Tukey–Kramer test using the NCSS 2000 statistical system for Windows. Differences with $P < 0.05$ were considered statistically significant.

RESULTS

Gross observations of dogs receiving no treatment and those receiving UC-II were recorded monthly during physical exam, and shown in Fig. 2. Dogs in Group 1, receiving no treatment, exhibited no change. In Group 2, all dogs receiving 1 mg UC-II/day for 90 days showed significant decreases in overall pain, lameness, and pain associated with limb manipulation. An increase in ability to exercise with less pain and lameness during the treatment period was also observed in Group 2. Upon 30 days withdrawal of UC-II, all dogs experienced significant increase in lameness, overall pain, and pain associated with limb manipulation (Fig. 2).

Following a 90-day treatment with UC-II (10 mg/day), dogs showed a significant decrease in pain when limbs were manually manipulated (Fig. 2). Dogs also experienced a significant decrease in their overall pain level during the 90-day treatment period. In addition, exercise-associated lameness was significantly reduced in all dogs. Overall, significant improvement was observed in all treatment groups. Following UC-II withdrawal for a period of 30 days, all dogs experienced a relapse of overall pain, exercise-associated lameness, and pain with limb manipulation (Fig. 2).

Data presented in Table 1 show that the values of BUN, creatinine, AST, and ALT were not significantly altered in serum of Group II or Group III dogs from the values of Group I dogs, suggesting no evidence of hepatic or renal injury, and that the UC-II was safe and well-tolerated by arthritic dogs.

DISCUSSION

Arthritis, the inflammation of joints, is a condition that afflicts dogs and humans alike. Healthy joints are not only important in

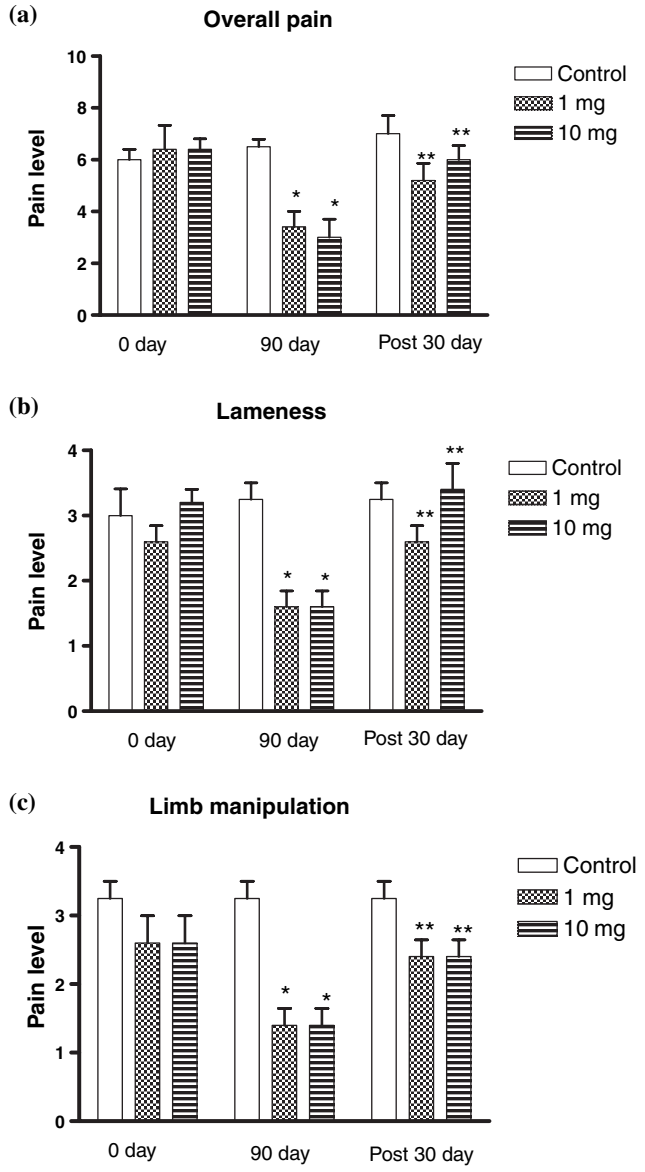

Fig. 2. Overall pain (a), lameness (b), and pain after physical exertion (c) in arthritic dogs receiving undenatured type-II collagen (UC-II) (1 mg/day or 10 mg/day) for 90 days. Overall pain was measured as a general gross observation, which included trouble in standing after sitting, or trouble in sitting after standing, vocalization, crying, etc. (results were graded on a scale of 0–10: 0, no pain; 5, moderate; 10, severe and constant pain). Pain during limb manipulation was evaluated by animals' vocalization or other observations of pain during the extension and flexion of all four limbs for few min (results were graded on a scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; 4, severe and constant). Lameness was measured after physical exercise for gross observations, which included limping, holding limb up, rigidity of limbs, etc. Signs of pain and lameness were noted on a scale of 0–4: 0, no pain; 1, mild; 2, moderate; 3, severe; 4, severe and constant). Results showed significant decreases in overall pain, and pain associated with lameness and limb manipulation. Withdrawal from UC-II for 30 days revealed a relapse in pain associated with lameness, overall pain, and pain with limb manipulation after physical exercise in all dogs. *Indicates significant difference between control (placebo) and UC-II treated dogs on day 90 ($P < 0.05$). **Indicates significant difference between the values of day 90 and postday 30 ($P < 0.05$).

the ability of dogs to perform well, but also for the comfort of dogs in routine movements such as walking, climbing stairs and rising from lying or sitting position. In several human clinical studies, Trentham and his colleagues have shown that undenatured type-II collagen works with the immune system to promote healthy joints and improve mobility and flexibility. In the first study, 6 of 10 arthritic patients taking type-II collagen for 90 days showed substantial improvement, while one patient recovered completely. No side effects were noted in any patients (Trentham *et al.*, 1993). In a follow-up 90-day double-blind, placebo-controlled study on patients with severe rheumatoid arthritis, 28 patients taking type-II collagen showed significant improvement compared to the placebo group, while four patients recovered completely (Nagler-Anderson *et al.*, 1986). In recent studies, several investigators have reported dramatic improvement in arthritic patients receiving UC-II with no side effects (Barnett *et al.*, 1996,1998; Sieper *et al.*, 1996). Therefore, the purpose of this investigation was to determine the therapeutic efficacy and safety of glycosylated undenatured cartilage derivative (UC-II) in arthritic dogs. Present results, as well as other supporting evidence, suggest that UC-II is a very effective dietary supplement in both arthritic dogs (Fig. 2) and humans (Trentham *et al.*, 2001; Bagchi *et al.*, 2002). With 1 mg daily UC-II treatment, Group 2 dogs were observed to be in significantly less pain while rising from a sitting or lying position, less pain during limb manipulation, and experienced less lameness after physical movement thus providing more range of activity such as walking, running, etc. (Fig. 2). In Group 3, dogs receiving 10 mg UC-II daily for 90 days showed significantly better physical improvement during the treatment period. These dogs responded positively in all aspects of physical evaluation (Fig. 2). In addition, dog owners observed an improved physical activity as the dogs were able to jog with their owners for miles without lameness for the first time in years. After the 30-day-withdrawal period, all dogs who had received treatment suffered from a relapse of signs and symptoms associated with arthritic conditions, such as pain and lameness.

In a recent investigation, time–dose vs. epitope exposure studies conducted on humans demonstrated that once UC-II is ingested, stomach acids and enzymes perform a partial digestion of the collagen matrix, resulting in chains of soluble collagen molecules of varying length containing biologically active epitopes (data not shown). The presence of these structurally precise natural epitopes in UC-II triggers a complex series of immunological events, which in the case of rheumatoid arthritis, down-regulates the body's out-of-control autoimmune response (Trentham *et al.*, 2001; Bagchi *et al.*, 2002). Furthermore, in the case of osteoarthritis, which is often characterized by a subclinical immune disorder and a vicious cycle of inflammatory events, UC-II promoted a reduction in inflammation (Bagchi *et al.*, 2002). Since UC-II is found to be effective in dogs and humans, it is presumed that the mechanisms described for humans may also hold true for dogs, although the exact biochemical mechanism(s) involved in UC-II-induced pharmacological anti-arthritic effects in dogs is yet to be elucidated. In the present study, we observed that the dogs that were unable to

Table 1. Biochemical parameters in serum of dogs receiving UC-II for 90 days

Parameters	Days			
	0	30	60	90
BUN (mg/dL)				
Control	18.80 ± 3.28	17.80 ± 1.85	19.60 ± 1.69	18.40 ± 2.87
1 mg	17.60 ± 2.29	15.20 ± 1.98	17.40 ± 2.70	13.20 ± 2.08
10 mg	13.60 ± 1.43	15.00 ± 1.22	19.40 ± 3.93	19.50 ± 4.77
Creatinine (mg/dL)				
Control	1.12 ± 0.07	1.12 ± 0.06	1.12 ± 0.10	1.04 ± 0.08
1 mg	1.22 ± 0.07	1.14 ± 0.06	1.18 ± 0.09	1.00 ± 0.07
10 mg	1.40 ± 0.18	1.18 ± 0.08	1.15 ± 0.03	1.42 ± 0.36
AST (IU/L)				
Control	24.00 ± 1.84	25.00 ± 2.49	26.00 ± 2.77	26.20 ± 1.36
1 mg	21.00 ± 2.12	19.20 ± 2.71	27.80 ± 7.15	26.00 ± 3.24
10 mg	18.80 ± 2.22	23.60 ± 1.47	25.50 ± 4.84	22.25 ± 4.17
ALT (IU/L)				
Control	28.00 ± 4.99	30.00 ± 3.24	28.80 ± 2.82	28.40 ± 3.59
1 mg	25.20 ± 2.75	21.80 ± 3.02	23.80 ± 3.07	21.00 ± 3.05
10 mg	30.00 ± 5.86	35.00 ± 5.37	32.50 ± 4.52	32.00 ± 11.68

Each value is the mean ± SEM ($n = 4–5$).
No value of day 30, day 60, or day 90 is significantly different from the value of day 0 ($P > 0.05$).
BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; UC-II: undenatured type-II collagen.

walk before receiving UC-II therapy became active and started running again. At either dose of UC-II, no adverse effects were observed in dogs and no significant change was noted in serum chemistry (BUN, creatinine, AST, and ALT) (Table 1). These findings suggest that no apparent effects were noted on liver/kidney, as evaluated by physical exam, history, and selected clinical chemistry. UC-II was well tolerated by arthritic dogs. It needs to be emphasized that there are no studies in the peer-reviewed literature showing that undenatured type-II collagen provides oral tolerization or relief of arthritis of any kind in dogs. In fact, there is one study that reports that denatured type-II collagen has no observable effect on the incidence and severity of the disease (Nagler-Anderson *et al.*, 1986).

CONCLUSIONS

Finding an effective cure for arthritis is a major challenge for veterinarians. Over the counter pain relievers, NSAIDs/other anti-inflammatory drugs (COX-I and COX-II enzymes inhibitors), and monoclonal antibodies have major adverse effects, including liver disease, gastritis, vomiting, and cardiovascular dysfunction. Results of the present study suggest that daily treatment of arthritic dogs with UC-II ameliorates signs and symptoms associated with arthritis, such as pain and lameness after physical exertion. The greatest physical improvements were noted after a treatment period of 90 days, suggesting that prolonged treatment with the supplement may lead to enhanced results. At either dose of UC-II, no adverse effects were noted, and no significant changes occurred in serum chemistry, and UC-II was well tolerated by arthritic dogs. In addition, the relapse seen in dogs 30 days post-treatment showed that continuous daily treatment of UC-II is required. Based on the present observations, future investigation needs to be conducted for a longer period to evaluate the effectiveness of UC-II on arthritic conditions in dogs. Finally, it is glycosylated undenatured type-II collagen, which is effective against arthritis and no adverse effects were noted and no significant changes occurred in serum chemistry. UC-II was safe and well tolerated in arthritic dogs.

ACKNOWLEDGMENTS

This investigation was supported by InterHealth Nutraceuticals Inc. and Beckman Coulter Inc. The authors thank Ms. Debra M. Britton and Ms. Shirley A. Zafra for their assistance in preparation of this manuscript.

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