

PGM 300mg/ml Inhalation Information

(Pentosan Polysulphate/Glucosamine Sulfate/MSM-Dimethyl Sulfone)

Pentosan polysulfate is a semi-synthetic molecule made from beechwood which shows some similarity in structure and charge to the endogenous glycosaminoglycans of connective tissues, including those present in cartilage (Burckhardt and Ghosh, 1987). It has some similarities to heparin, though it is smaller, more highly charged and not as potent as an anticoagulant. These properties allow pentosan polysulfate to localize within the extracellular matrix and directly influence enzymatic and cellular events over a longer period than most other drugs. This reduces considerably the frequency of treatment and thus side-effects.

Pentosan effectiveness

A double-blind trial using pentosan polysulfate was undertaken in 43 patients with knee arthrosis of Severity I and II (Engel & Juhran, 1982). After a washout period of three days, the drug (100mg) was administered intramuscularly to half the group according to the following protocol: days 1-3, one injection (100mg) daily; day 4, no drug treatment; Days 5-27, one injection (100mg) every second day. This represented a total of 15 injections or 1500mg of pentosan polysulfate or the placebo solution. The patient response was assessed using a 1-5 pain scale of both subjective and objective criteria which included pain at rest, pain during movement, activity limitation of movement, passive limitation of movement and pain caused by fatigue. Overall assessment by the physician and patients on a weekly basis showed an improvement in all clinical criteria measured over the four week study period in the drug-treated group relative to the placebo group.

A double-blind, placebo-controlled clinical study in 105 patients with osteoarthritis of the knee has been performed in Perth, Australia (Edelman et al. 1994) where patients either received a salt solution or pentosan polysulphate at 3mg/kg as an intramuscular injection once weekly for 4

weeks. In the pentosan polysulphate treated patients, stiffness significantly improved after the first week and pain on walking or at rest, time to walk upstairs and overall pain significantly improved after the first month. Pain at rest and step time were still significantly better than the placebo group after 2 months.

Pentosan polysulphate is currently undergoing double-blind clinical trials for the management of the osteoarthritis patient in a number of countries.

A preliminary report has been published (Rasaratnam et al., 1996) of a double-blind placebo controlled study of intra-articular pentosan polyfulphate (0 or 50mg per joint once weekly for 4 weeks) in 50 patients suffering osteoarthritis of the knee. Even with 31 of the 50 patients evaluated, there were significant improvements in pain and mobility for up to 2 months after completing the treatment.

Extensive veterinary application of this drug over the last ten years for the treatment of traumatic and geriatric osteoarthritis in dogs has demonstrated clinical effectiveness in this species.

The pathobiology of osteoarthritis and the rationale for the use of pentosan polysulfate for its treatment.

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OBJECTIVES: Structure-modifying osteoarthritis (OA) drugs (SMOADs) may be defined as agents that reverse, retard or stabilize the underlying pathology of OA, thereby providing symptomatic relief in the long-term. The objective of this review was to evaluate the literature on sodium pentosan polysulfate (NaPPS) and calcium pentosan polysulfate (CaPPS), with respect to pathobiology of OA to ascertain whether these agents should be classified as SMOADSs. **METHODS:** Published studies on NaPPS and CaPPS were selected on the basis of their relevance to known pathobiology of OA, which also was reviewed. **RESULTS:** Both NaPPS and CaPPS exhibit a wide range of pharmacological activities. Of significance was the ability of these agents to support chondrocyte anabolic activities and

attenuate catabolic events responsible for loss of components of the cartilage extracellular matrix in OA joints. Although some of the anticatabolic activities may be mediated through direct enzyme inhibition, NaPPS and CaPPS also have been shown to enter chondrocytes and bind to promoter proteins and alter gene expression of matrix metalloproteinases and possibly other mediators. In rat models of arthritis, NaPPS and CaPPS reduced joint swelling and inflammatory mediator levels in pouch fluids. Moreover, synoviocyte biosynthesis of high-molecular-weight hyaluronan, which is diminished in OA, was normalized when these cells were incubated with NaPPS and CaPPS or after intra-articular injection of NaPPS into arthritic joints. In rabbit, canine, and ovine models of OA, NaPPS and CaPPS preserved cartilage integrity proteoglycan synthesis, and reduced matrix metalloproteinase activity. NaPPS and CaPPS stimulated the release of tissue plasminogen activator (t-PA), superoxide dismutase and lipases from vascular endothelium while concomitantly decreasing plasma levels of the endogenous plasminogen activator inhibitor PAI-1. The net thrombolytic and lipolytic effects exhibited by NaPPS and CaPPS may serve to improve blood flow through subchondral capillaries of OA joints and improve bone cell nutrition. In geriatric OA dogs, NaPPS and CaPPS reduced symptoms, as well as normalized their thrombolytic status, threshold for platelet activation, and plasma triglyceride levels. These hematologic parameters were shown to be abnormal in OA animals before drug treatment. Similar outcomes were observed in OA patients when CaPPS or NaPPS were given orally or parenterally in both open and double-blind trials. **CONCLUSIONS:** The data presented in this review support the contention that NaPPS and CaPPS should be classified as SMOADs. However, additional long-term clinical studies employing methods of assessing joint structural changes will be needed to confirm this view.

Publication Types:

Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers.

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OBJECTIVE: To determine whether glucosamine sulfate has an effect on cartilage type II collagen degradation in patients with knee osteoarthritis (OA). **METHODS:** A randomized, double-blind, placebo controlled glucosamine discontinuation trial was conducted in 137 subjects with knee OA, who had had at least moderate relief of knee pain after starting glucosamine. Subjects were randomized to glucosamine at pre-study dose or placebo at an equivalent dose. Treatment was continued to Week 24 or disease flare, whichever occurred first. Serum and urine samples were collected at Weeks 0, 4, 12, and 24 or flare visit. Samples were analyzed in triplicate for 2 type II collagen degradation biomarkers: C2C epitope (COL2-3/4C(long)) and C1,2C epitope (COL2-3/4C(short)). The primary outcome was the mean change in serum and urine C1,2C/C2C ratio in the glucosamine and placebo groups from baseline to final (flare or Week 24) visit. Linear regression analyses were conducted to adjust for potential confounders. Due to non-normal distributions, the data were log-transformed ($\ln C1,2C/C2C$). Secondary outcomes included comparison of mean change scores at final visit compared to baseline for serum and urine C1,2C and C2C in the 2 treatment groups and in Flare versus No-Flare groups. **RESULTS:** Baseline and final visit samples were available in 130 subjects for serum analysis and 126 subjects for urinalysis. No significant difference was seen between placebo and glucosamine groups in the serum C1,2C/C2C ratio, with a mean (SD) change from baseline to final visit of 0.8 (27.8) and -0.1 (1.8), respectively (mean difference 0.9; 95% CI - 6.0, 7.7, $p=0.80$). Similarly, no differences between treatment groups were seen for mean change in urine C1,2C/C2C ($p=0.82$), or for mean change in C2C or C1,2C. In linear regression analysis, after adjustment for sex, radiographic severity, baseline $\ln C1,2C/C2C$ ratio, WOMAC function, and flare status,

treatment was not a significant predictor of final serum or urine lnC1,2C/C2C ratio. When those who experienced flare were contrasted with those without flare, there was a nonsignificant trend toward a difference in mean baseline to final visit change score for serum C1,2C/C2C ratio ($p=0.16$). CONCLUSION: No statistically significant effect of glucosamine sulfate on type II collagen fragment levels in serum or urine was observed for knee OA over 6 months. Further research is necessary to elucidate which biopathologic systems, if any, are affected by glucosamine treatment. While collagen degradation products may be of value in predicting progression, at least as defined by clinical flare, a larger dataset would be needed to prove this.

MSM

MSM is also known as dimethyl sulfone. The sulfur compound is a nutrient found in the human diet and the natural diets of virtually all other vertebrates. It is odorless and in its purified chemical form, it is water-soluble, white crystalline solid. It belongs in the same chemical family as oxygen, and in oxygen depleted environments, sulfur often replaces oxygen as the source of chemical energy upon which life thrives. It's a dietary supplement that does not require a prescription. A daily dose of 1000mg is common, and for some conditions, doses as high as 2 to 6 grams may be appropriate.

MSM is rated as one of the least toxic substances in biology. Common table salt is much more toxic than MSM. However, some individuals have reported a "detox" reaction that passes in one to two days.

Researchers at OHSU studied a strain of mice that were prone to spontaneous development of joint lesions similar to those in rheumatoid arthritis (14). They found animals that were fed a diet that included a 3% solution of MSM in drinking water from the age of two months until the age of five months suffered no degeneration of articular cartilage. In a control group of mice receiving only tap water, 50% of the animals were found to have focal generation of articular cartilage.