ARTHRITIS & RHEUMATISM
Vol. 41, No. 5, May 1998, pp 939–941

CONCISE COMMUNICATIONS

Pseudogout following intraarticular injection of sodium hyaluronate

Sodium hyaluronate is a natural substance that acts as a lubricant and shock-absorber in joints. Its use has recently been indicated for relief of knee pain due to osteoarthritis (OA) in patients who do not obtain adequate relief from simple analgesics or nonsteroidal antiinflammatory drugs, or from exercise and physical therapy. It is given as an intraarticular injection in a course consisting of 1 injection weekly for 5 weeks, for a total of 5 injections. Strict aseptic technique is used for the injection. Joint effusion, if present, must be removed before sodium hyaluronate is injected. The patient should avoid any strenuous activities or prolonged weight-bearing activities within 48 hours after the injection.

Contraindications to sodium hyaluronate treatment include known hypersensitivity to hyaluronate preparations, or any infection or skin disease in the area of the injection site. Reported side effects include gastrointestinal symptoms, pain at the injection site, knee swelling/effusion, local skin reactions (rash, ecchymosis), pruritus, headache, and fever. The symptoms are mild and resolve in a short time. Allergic reactions and transient increases in inflammation in the injected knee following sodium hyaluronate injection have been reported in some patients with inflammatory arthritis such as rheumatoid arthritis or gouty arthritis. To date, there have been no reports of acute attacks of pseudogout following an injection of sodium hyaluronate. Herein we describe the occurrence of this complication in a man who underwent sodium hyaluronate injection for severe OA-associated knee pain.

The patient was a 52-year-old man with severe OA involving the neck at levels C4–C7, lumbar spine at levels L3–L4 and L4–L5 with laminectomy at L5–S1, and both knees. He had a lengthy history of severe pain in his knees (onset after a high school injury when he tore his right knee meniscus) and back. He had undergone multiple surgeries: 5 on the right knee and 2 on the left knee (arthrotomy for torn cartilage, ligament repair, tibial osteotomy, medial and lateral meniscal removal with debridement) and various types of therapy including antiinflammatory drugs, muscle relaxants, physical therapy, back exercises, and steroid injections.

The patient presented with bilateral knee pain, which was greater on the right side. Examination showed crepitation with flexion and extension of the knees and a small amount of fluid, as confirmed by a positive bulge sign in both knees. No warmth, redness, or tenderness was present. Previous knee radiographs showed severe OA with almost complete loss of the medial cartilage, but no chondrocalcinosis.

After giving informed consent, the patient underwent intraarticular injection of sodium hyaluronate (Hyalgan; Sanofi Pharmaceuticals, New York, NY) in both knees, under aseptic conditions. The knees were aspirated before injection of the drug, and local lidocaine anesthesia was used. The procedure was accompanied by mild bleeding, but no other problems. One week later, a second injection was performed in each knee, with local lidocaine anesthesia. Aspiration was not necessary. The procedure was again done under strict aseptic conditions, and was performed with no difficulty.

Twenty-four hours later, the patient developed severe pain and right knee inflammation. There was no fever, chills, fall, injury, locking, buckling, tingling, or numbness. He had mild discomfort in the left knee. Examination showed moderate effusion of the right knee, with mild warmth but no redness. Arthrocentesis was performed, and showed many white blood cells and many calcium pyrophosphate dihydrate (CPPD) crystals, mostly intracellular, indicating pseudogout. Numerous rhomboid crystals were seen, along with blunt-ended linear crystals. Using a first-order red compensator, these were confirmed to be weakly positively birefringent. Gram stain revealed many polymorphonuclear leukocytes, but no evidence of bacteria. Synovial fluid (SF) cell counts were as follows: 8,200 red blood cells/μl and 13,950 white blood cells/μl, with 82% polymorphonuclear leukocytes. Treatment with controlled-release naproxen sodium was immediately started, with complete resolution of inflammation within 7 days. Final cultures were negative. The patient declined any further sodium hyaluronate injections.

This is the first description of an acute attack of pseudogout arthritis immediately following sodium hyaluronate injection. Physicians should be aware of this possibility. This occurrence was reported to Sanofi Pharmaceuticals. Sanofi reported to us that surveillance data showed no reports of gout or pseudogout following sodium hyaluronate injection in the US. Two reports of gout occurring after sodium hyaluronate injection were received from European studies, but one occurred >300 days postinjection, and the other was not confirmed by microscopic identification of the crystals. Several cases of acute inflammation postinjection were considered to be infections and were treated as such, though they were later shown to be culture negative. In these cases, it was unclear if any microscopic examination for gout or pseudogout crystals was performed (Goldsmith DI: Sanofi Pharmaceuticals: personal communication).

If an acute inflammatory arthritis occurs after sodium hyaluronate injection, a comprehensive approach to diagnosis should be undertaken, as for any acutely inflamed joint. Several reports of pyogenic arthritis following sodium hyaluronate injection are mentioned in the product information literature. We initially were concerned that our patient had postinjection joint sepsis, but fortunately this was not the case. Since we routinely perform a complete evaluation of the SF in any acutely inflamed joint, admission to the hospital and intravenous antibiotic therapy were avoided. This resulted in a significant decrease in potential medical expenditure.

Our patient had no previous episodes of crystal-induced arthritis. The onset of the pseudogout attack occurred within 24 hours of the sodium hyaluronate injection. Shedding of CPPD crystals can be a complication of various joint procedures, and we postulate that sodium hyaluronate caused shedding of CPPD crystals from storage areas in the synovium or cartilage and precipitated this attack. However, the mechanism by which sodium hyaluronate could precipitate acute pseudogout is unclear. The formation of CPPD crystals usually occurs in the midzone of hyaline cartilage, and less often in the synovial membrane (1). Pyrophosphate levels are usually increased in the SF of patients with CPPD deposits. An in-

creased pyrophosphate concentration in SF may also be a result of increased protoglycan synthesis. Changes in pyrophosphatase or alkaline phosphatase levels within the joint may affect crystallization (1).

There are several postulated mechanisms of action of hyaluronan. The effects of hyaluronan last much longer than the actual time the substance resides in the joints. The effects occur possibly at 3 levels: the macroscopic level, the mini-homeostasis level, and the micro-homeostasis level. At the macroscopic level, the hyaluronan injected may provide stabilization and protection of the collagen fibrous network, the cells, and the pain receptors. Mini-homeostasis involves trans–synovial fluid flow. In OA, where the elastoviscosity of hyaluronan is lower than normal, trans–synovial fluid flow may be up to 4 times faster than in normal subjects. Viscosupplementation increases elastoviscosity of the fluids and restores homeostasis of trans–synovial fluid flow in the joints. Micro-homeostasis refers to the microenvironment of the joint, including cells and sensory fibers. Viscosupplementation restores the microhomeostasis of the joint. After supplementation, the hyaluronan-synthesizing cells are surrounded by a new microenvironment which simulates their own hyaluronan synthesis, maintaining restored microhomeostasis. Viscosupplementation may also inhibit the diffusion of destructive enzymes into the cartilage (2).

The increased synthesis of proteoglycans after hyaluronan injection could affect pyrophosphate concentrations in the synovial fluid, or somehow otherwise affect pyrophosphate levels and precipitate attacks. Hyaluronan injection could possibly affect the ionic concentrations of calcium, magnesium, and phosphates enough to mobilize CPPD crystals into the joint and initiate an acute attack. At this time, however, the mechanisms by which hyaluronan might precipitate CPPD attacks are unclear.

Any acute inflammation of a joint after sodium hyaluronate injection should be approached in a comprehensive manner. Based on the finding of CPPD crystals in our patient, we believe the evaluation should include complete analysis of joint fluid for infection or crystals.

Michael J. Luzar, MD
Northeastern Ohio Universities College of Medicine and Western Reserve Care System
Youngstown, OH
Badi Altawil, MD
Western Reserve Care System
Youngstown, OH

1. Reginato AJ, Reginato AM. Diseases associated with deposition of calcium pyrophosphate or hydroxyapatite. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge C, editors. Textbook of rheumatology. 5th ed. Philadelphia: WB Saunders; 1997. p. 1358–62.
2. Balazs E, Denlinger JC, Viscosupplementation, a new concept in the treatment of osteoarthritis. J Rheumatol 1993;20 suppl 39:3–9.

The polymorphic CYP17 allele is not found with increased frequency in systemic lupus erythematosus

The demographics of systemic lupus erythematosus (SLE) suggest that there are profound hormone effects. The prevalence of SLE is approximately 10 times higher in women than in men, with the majority of cases occurring during the childbearing years (1–5). This sex differential is less pronounced prior to puberty and after menopause. In addition, oral contraceptive use and estrogen replacement therapy appear to confer a risk for development of SLE. These data and findings from experimental animal studies suggest that estrogen promotes the occurrence of SLE. Furthermore, some men who develop SLE have evidence of hypoandrogenism, suggesting that androgens may be protective against the development of SLE (6). We hypothesized that inherited genetic polymorphisms that affect hormone production or regulation might be associated with an increased predisposition to SLE.

Table 1. CYP17 A2 gene frequencies in systemic lupus erythematosus (SLE) and control populations

Study population	n	Gene frequency	*P*
All SLE patients	115	0.442	0.127
All controls	143	0.381	
African American SLE patients	51	0.412	0.506
African American controls	71	0.366	
White SLE patients	64	0.477	0.220
White controls	72	0.396	
Female SLE patients	106	0.442	1.00
Male SLE patients	9	0.444	

The CYP17 gene encodes the cytochrome P450c17α enzyme, which is essential for both adrenal and gonadal steroid biosynthesis. Deficiency of P450c17α results in congenital adrenal hyperplasia (7). In the adrenal gland, P450c17α regulates cortisol production, and its expression is adrenocorticotropic hormone dependent (8). In testicular Leydig cells, P450c17α catalyzes the conversion of progesterone to androstenedione, which can subsequently be converted to testosterone (8). This process is regulated at the level of transcription and is cAMP dependent (9). In ovarian thecal cells, P450c17α expression is transcriptionally regulated in response to luteinizing hormone via cAMP (10).

Recently, a common polymorphism was identified in the promoter of the CYP17 gene, at −34 basepairs (11). This polymorphism occurs in a region of the promoter thought to be important in the transcriptional regulation of CYP17 in response to cAMP (8,10). The single base change, a T to C transition, denoted as the A2 allele, creates a potential site for the binding of the SP1 transcription factor in a region of the promoter that is important for cAMP-responsive transcription. This polymorphism has been thought to result in increased production of P450c17α and of gonadal steroids such as estrogen and testosterone.

Several studies have evaluated the role of this CYP17 polymorphism in human disease. An increased frequency of this allele has been found in patients with polycystic ovary syndrome and patients with breast cancer, suggesting that inheritance of this allele may modulate hormone production such that overall estrogen production is increased (11,12). Supporting this hypothesis is the finding that women who have inherited the A2 allele have earlier menarche, consistent with increased estrogen production (12). Although other studies