

Case Report

Induction of an Acute Attack of Calcium Pyrophosphate Dihydrate Arthritis by Intra-articular Injection of Hylan G-F 20 (Synvisc)

S. Kroesen, W. Schmid and R. Theiler

Rheumaklinik und Institut für Physikalische Medizin, Kantonsspital Aarau, Aarau, Switzerland

Abstract: Little is known about the induction of acute calcium pyrophosphate dihydrate arthritis after the intra-articular injection of hylan G-F 20 (Synvisc). Two reports have documented this adverse effect after the intra-articular injection of hyaluronan. Our patient, a 60-year-old man with osteoarthritis in both knees, presented with a history of an arthroscopy with meniscus shaving 7 years previously. He was given an injection of hylan G-F 20 in the right knee joint. Two days after the second injection, pain and swelling of the knee occurred. There was a severe loss of physical function. Systemic inflammatory reactions such as fever were not observed. A microscopic investigation of the synovial fluid showed evidence of calcium pyrophosphate dihydrate crystals. Bacterial contamination was not detected. There was no indication for calcium pyrophosphate dihydrate in the history of the patient. Some days after receiving non-steroidal anti-inflammatory drugs and an intra-articular injection of steroids, the symptoms disappeared.

Keywords: Calcium pyrophosphate dihydrate arthritis; Hylan G-F 20; Side-effects; Viscosupplementation

Introduction

In several studies of viscosupplementation in osteoarthritis (OA) therapy, few side-effects are mentioned [1,2], although some studies have reported transient effects such as swelling or increased pain in the treated joint [3,4]. These effects lasted for only a few days and seemed to be connected to the method of application. In

Correspondence and offprint requests to: R. Theiler, Rheumaklinik und Institut für Physikalische Medizin, Kantonsspital Aarau, CH 5001 Aarau, Switzerland. Tel: 0041/62/838 46 92; Fax: 0041/62/838 46 30.

all of the randomised controlled trial (RCT) studies mentioned above, the patients in the control group also presented such symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs) and cool pack therapy were sufficient for pain relief. Only a small number of severe side-effects have been reported, such as haemarthrosis [5], transient increase of transaminases [6], phlebitis [7], itching and cramps [8], restless leg and vertigo [9], and finally calcium pyrophosphate dihydrate (CPPD) crystals [10,11]. The most important differential diagnosis of CPPD arthritis is septic arthritis of the treated joint, which causes severe consequences for the patient and for the physician. To date, there has been only one case of septic arthritis reported in a trial of hyaluronan [12]. However, three cases have been reported where an acute attack of CPPD arthritis was induced after treatment with hyaluronan (Table 1). We report a case of CPPD arthritis after an injection of hylan G-F 20.

Case Report

A 60-year-old man presented with OA of both knees. Seven years previously, arthroscopy with meniscus shaving had been performed in the right knee. There was no history of crystal arthropathy. Radiography did not document any signs of cartilage calcification and the family history was negative for CPPD arthritis. The patient did not have any of the CPPD-associated diseases such as haemochromatosis, hyperparathyroidism, hypophosphatasia, hypocalcaemia, hypomagnesaemia or hypothyroidism.

During the first treatment with hylan, aspiration was not necessary because there was no effusion in this knee and the drug was injected under aseptic conditions. The

Table 1. Comparison of four patients suffering from severe side-effects after treatment with hyaluronan

Reference	Age/gender	History	Symptoms	X-ray	Arthrocentesis
Maillefert et al. (1997) [10]	83 years Female	OA right knee, 1 cycle of five injections of hylan, well tolerated	6 h after the 2nd injection of the 2nd cycle: pain, swelling in the right knee, loss of physical function, temperature 38°C, increase of CRP and ESR	After complications, chondrocalcinosis was diagnosed	Elevated cell count, >90% neutrophils, CPPD crystals, no bacteria
Maillefert et al. (1997) [10]	62 years Female	OA left knee, post-meniscectomy re	5 h after 1st injection: increased pain, decreased function of left knee, fever 38.5°C	Chondrocalcinosis after treatment	Declined by the patient
Luzar & Altawil (1998) [11]	53 years Male	OA both knees, injury of meniscus re in youth, a lot of knee surgery (right 5, left 2), hylan both knees, no history of crystal arthropathy	24 h after 2nd injection: increasing pain, swelling, loss of function	Previously no chondrocalcinosis	13 950 leucocytes/ μ l 82% neutrophils, CPPD crystals, no bacteria
Kroesen et al. (1999) [this study]	60 years Male	OA both knees, arthroscopy with meniscus shaving in the right knee in 1991	2 days after 1st injection: increased pain, swelling, loss of function	Previously no chondrocalcinosis	9270 leucocytes/ μ l 50% neutrophils CPPD crystals, no bacteria

OA, osteoarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CPPD, calcium pyrophosphate dihydrate; re, right.

treatment was well tolerated. The second course was performed as for the previous course, 1 week later. Two days after the second injection, the patient developed very painful swelling, redness and loss of physical function in the right knee. Neither fever nor systemic signs of inflammation was observed, therefore a blood sample was not taken. After the clinical investigation, an arthrocentesis was performed and the synovial fluid was analysed.

There was no bacterial contamination. The number of leucocytes in the synovial fluid had increased to 9270 per microlitre with 50% neutrophils. Many intracellular rhomboid crystals were depicted, defined as CPPD crystals. After this complication, radiography was not performed because the diagnosis was definitively an acute attack of CPPD arthritis.

The patient was treated with NSAIDs. Three days later, the symptoms had significantly diminished. A few days later, after an intra-articular injection of steroid (triamcinolone acetate, 40 mg), the symptoms had disappeared.

Discussion

Until now, the concept of viscosupplementation with hyaluronan has been as a disease-modifying strategy to treat painful OA. This intervention seems to be generally well tolerated by patients. Reduction of pain and an improvement of physical activity after a few injections can last for several months. Especially elderly people, with a baseline algofunctional Lequesne index greater than 10, may benefit from this treatment [13].

Several studies have shown no serious side-effects of this treatment. However, other studies have described side-effects, which were seen in the context of an intra-articular injection. Some severe side-effects have been reported, which could probably relativate the success of viscosupplementation. Puttick et al. [14] investigated the acute local reactions after viscosupplementation; 28 knees were punctured and significant local inflammation was observed in 27% of the patients. One patient showed antibodies to avian proteins suggesting an allergic reaction, and another presented CPPD crystals on radiograph before the treatment. The other patients showed neither bacterial contamination nor crystal arthritis.

Little is known about the induction of acute CPPD arthritis after the intra-articular injection of hyaluronan. To date, three cases have been reported in the literature. Pain and swelling of the joint was accompanied by fever. All of the patients showed an increase of leucocytes with a high percentage of neutrophils and CPPD crystals in the synovial fluid. Owing to the severity of symptoms, an interruption of this therapy was necessary. It is probable that the number of patients suffering from reactive side-effects in the daily routine is much higher than that mentioned in the literature.

Although four cases cannot provide strong evidence, a comparison of these four cases of induced CPPD shows some similarities. Further work is needed to obtain strong data on this side-effect.

The first finding is the time point at which the symptoms occur. In each patient the attack occurred several hours or a few days after the second injection. Therefore, a sensitisation period or an allergic reaction

seems to be necessary to produce these symptoms. This finding is also of interest for investigating the possible pathomechanism. Until now, little has been discovered about the method of induction.

The second finding is the association with meniscectomy or some other surgery in the treated knee. There is a correlation between developing symptoms of CPPD and a history of meniscectomy.

The third finding is the correlation between CPPD and the age of the patients. There is evidence that CPPD crystals were found in the synovia, cartilage and periarticular tissues, especially in elderly patients without symptoms of pseudogout. However, it could be postulated that these patients develop a CPPD arthritis because of the intra-articular injection of hyaluronan. Lohmander et al. [13] have pointed out that this group of patients derive the best benefit from being treated with hyaluronan. In their study, induction of CPPD was not reported.

Conclusion

The induction of CPPD arthritis after an intra-articular injection of hyaluronan has been documented in four cases in the literature. It is possible that there are many more patients with these symptoms than are mentioned in the literature. These symptoms are very similar to those of septic arthritis. However, the symptoms could be due to an allergic reaction. For the clinician, it would be very helpful to avoid such side-effects. It is not known if the type of hyaluronic acid could play a pathophysiological role in this context.

Acknowledgement. This work was supported by a grant from the 'Hugo and Elsa Isler Foundation/Aarau'.

References

1. Leardini G, Mattara I, Franceschini M, Perbellini A. Intraarticular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. *Clin Exp Rheumatol* 1991;9:375-80.
2. Leardini G, Perbellini A, Franceschini M, Mattara L. Intraarticular injections of hyaluronic acid in the treatment of painful shoulder. *Clin Ther* 1988;19:521-5.
3. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26 week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther* 1998;20:410-23.
4. Henderson E, Smith E, Pegley F, Blake D. Intraarticular injection of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single center, double-blind, placebo controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis* 1994;53:529-34.
5. Puhl W, Bernau A, Greiling H, Kopcke W, Pforringer W, Steck KJ, et al. Intraarticular sodium hyaluronate in osteoarthritis of the knee: a multicentre, double-blind study. *Osteoarthritis Cart* 1993;1:233-41.
6. Oshima Y. Intra-articular injection therapy of high molecular weight sodium hyaluronate in osteoarthritis of the knee joint. Phase II clinical study. *Jpn Pharmacol Ther* 1983;11:2253-7.
7. Dixon AS, Jacoby RK, Berry H. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Curr Med Res Opin* 1988;11:205-13.
8. Adams ME, Atkinson MH, Lussier AJ, Schultz HI, Siminovitch K, Wade JP, Zummer M. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicentre trial comparing hylan F-F 20 alone, hylan G-F 20 with NSAIDs and NSAIDs alone. *Osteoarthritis Cart* 1995;3:213-26.
9. Honma T. Clinical effects of high molecular weight sodium hyaluronate (ARTZ) injected into osteoarthritic knee joints. *Jpn Pharmacol Ther* 1987;17:5057-72.
10. Maillefert JF, Hirschhorn P, Pascaud F, Piroth C, Tavervier C. Acute attack of CPPD after an intraarticular injection of hyaluronan. *Rev Rheum* 1997;10:593-4.
11. Luzar MJ, Altawil B. Pseudogout following intraarticular injection of sodium hyaluronate. *Arthritis Rheum* 1998;41:939-40.
12. Christenson RCL, Dahlberg L, Lohmander S. *Candida albicans* arthritis in a non-immunocompromised patient. Complication of placebo intraarticular injection. *Acta Orthop Scand* 1993;64:696-8.
13. Lohmander L, Dalen N, Englund G, Hamalainen M, Jensen E, Karlsson K, et al. Intra-articular hyaluronan injection in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Ann Rheum Dis* 1996; 55:424-31.
14. Puttick M, Wade J, Chalmers A, Connell D, Tangno K. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. *J Rheumatol* 1995;22:1311-4.

Received for publication 4 February 1999

Accepted in revised form 25 August 1999