LONG-LASTING ANALGESIC EFFECT OF INTRA-ARTICULAR INJECTION OF CROSS-LINKED HYALURONATE HYDROGEL (GEL-200) ON ARTHRITIC PAIN

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Introduction:
The arthritic pain model used in this study is a local pain model produced by injecting bradykinin (an endogenous hyperalgesic substance) with PGE2 (a pain enhancer) into the joint cavity of rats (1). This model has been used to assess the analgesic effects of hyaluronan preparations based on the behavioral manifestations of joint pain in gait such as “lifting the foot”, “claudication” and “walking on three legs”. It has been reported that the analgesic effect assessed by this model was associated with the concentration of hyaluronan in synovial tissue (2).

The objective of this study was to examine the long-lasting analgesic effect and local retention of intra-articularly injected cross-linked hyaluronate hydrogel (Gel-200), which has been developed as a novel therapeutic agent for the knee osteoarthritis (OA).

Methods:
1) Determining the effects of Gel-200 on the bradykinin-induced arthritic pain in rats.
Gel-200, physiological saline or SUPARTZ® was administered into the knee joint cavity of the left hind leg of female rats at a dose of 0.05 mL/joint. On weeks 1, 2 and 4 after administration, bradykinin solutions were injected into the same joint to induce arthritic pain. SUPARTZ® was only evaluated at 1 week, since this treatment typically requires reinjection once a week. Under blinded conditions, the walking of the animal was observed for about 2 minutes after injection of bradykinin solutions and severity of pain was scored on a 5-point scale.

2) Determining the residual ratio of Gel-200 in joint cavity and synovium of the knee in rabbits.
Gel-200 and its non-cross-linked intermediate (h-HAD), were administered into the knee joint cavity in male rabbits at a dose of 0.05 mL/kg/joint. Animals were sacrificed on days 1, 3, 5, 7, 14 and 28 after administration, and synovial fluid and synovium were collected. The common cross-linked agent was quantified by high performance liquid chromatography (HPLC) to calculate the residual ratios of Gel-200 and h-HAD.

Results:
1) Gel-200 significantly suppressed the bradykinin-induced pain response compared with control group at the time points 1, 2 and 4 weeks post administration (Figure 1). The analgesic effect by Gel-200 was more remarkable than that by SUPARTZ® at 1 week.

2) Most of Gel-200 disappeared from the synovial fluid within 7 days, however, it remained in the synovium for up to 28 days after administration (Figure 2 and 3). By comparing the residual ratios of Gel-200 and h-HAD, significantly higher levels of Gel-200 were detected in the synovial fluid on days 1, 3 and 5 after administration. However, in the synovium, the ratios of Gel-200 remained significantly higher on days 7, 14, and 28. The results with h-HAD were similar to those reported previously using C-hyaluronan (3).

Conclusions:
It was demonstrated that Gel-200 administered into the joint cavity was more effective against the arthritic pain than SUPARTZ® and provided a sustained analgesic effect lasted for at least 4 weeks. Furthermore, compared to non-cross-linked hyaluronan, the injected Gel-200 remained in synovial fluid and synovium for a prolonged period of time. Consequently, since Gel-200 remains in the joint cavity longer, and is incorporated into the synovium slowly, it is speculated that Gel-200 exerts a long-lasting analgesic effect.

References:

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