The Effect of Intra-Articular Gadolinium-DTPA on Synovial Membrane and Cartilage

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This investigation evaluated the potential effect of gadolinium (Gd)-DTPA-dimeglumine on synovial membrane and joint cartilage, using macroscopic, microscopic, and x-ray fluorescent spectroscopic techniques. Thirteen New Zealand white rabbits (26 knees) were used in this study, ten receiving 500 micromolar injections of Gd-DTPA-dimeglumine in their right knees; the remainder of the knees served as controls. One injected knee had minimal joint effusion and one had mild hyperemia. Microscopically four knees exhibited mild focal hyperplasia of the synovium, another three minimal focal mononuclear cell infiltration. X-ray fluorescent spectroscopy demonstrated no evidence of Gd-DTPA-dimeglumine in the synovium or articular cartilage. Neither macroscopic nor microscopic evaluation detected any Gd-DTPA-dimeglumine related effects. Gd-DTPA-dimeglumine was found to be safe for intra-articular injection in this animal model.

key words: MRI; joint cartilage; joint synovium; Gd-DTPA-dimeglumine.

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RECENT INVESTIGATIONS have emphasized the capabilities of magnetic resonance imaging (MRI) to delineate normal and abnormal articular structures.[1–5] Furthermore, visualization of articular structures is enhanced by the presence of intra-articular fluid.[6] In the absence of an effusion, iatrogenically introduced fluid (a procedure termed magnetic resonance [MR] arthrography) can increase the diagnostic value of MRI because articular cartilage, joint capsule, and smaller (but nevertheless clinically important) anatomic structures cannot be reliably demonstrated without an intra-articular contrast agent.[6]

As we have shown in previous studies, 500 μmol of gadolinium (Gd)-DTPA is an ideal intra-articular contrast agent for spin-echo imaging, because it provides excellent contrast to all anatomic structuress.[6,7] To date, only minor side effects have been reported after intravenous injection of Gd-DTPA-dimeglumine (Magnevist, Schering AG, Berlin, West Germany) in concentrations below 0.5 μmol/kg. The absence of anaphylactoid reactions and a short half-life in blood and urine support high in vivo tolerance of this contrast agent.[8–11] The goal of this study is to describe the gross pathologic and histologic alterations induced by intra-articular 500 μmol of Gd-DTPA-dimeglumine in rabbit synovium and joint cartilage.

Materials and Methods

Thirteen New Zealand white rabbits (26 knees) weighing 3 kg to 4 kg were used in this investigation (Table 1). Two milliliters of 500 μmol solution of Gd-DTPA-dimeglumine (pH 7.2) were

injected into the right knee of ten animals. Two milliliters of 0.9% (wt/vol) physiologic saline solution were injected into the left knees of seven of the same animals to establish the effect of articular distension on synovium and cartilage. The other three left knees of these ten animals were punctured without injection to establish the effect of needle puncture alone. The animals with knees injected with Gd-DTPA-dimeglumine (right knee), saline solution (left knee), or needle puncture (left knee) were sacrificed after either 2, 6, 12, or 24 hours or eight days. (Two animals sacrificed at each interval.) Uninjected animals were sacrificed at 24 hours, 72 hours, and eight days after needle puncture. The synovium and articular cartilage of each knee were excised and stained with hematoxylin and eosin. The pathologist had no knowledge of the material injected nor how long after injection the animals had been killed. In addition, samples of the synovium and cartilage were homogenized using a high-speed cutting blade device tissumizer (Tekmar, Inc, Cincinnati, OH) until an even consistency was achieved. Tissue standards of 1, 10, 20, 40, 70, 100, 200, 300, and 400 μmol/L Gd-DTPA-dimeglumine concentrations were prepared as standards. Samples were mounted over a thin film made of Formivar Powder (Ladd Catalog 10835 15/95 Grade) on a 2-inch by 2-inch slide (Pac Slide Mounts, Minneapolis, MN). After the slides dried, x-ray fluorescent spectroscopy was performed using a Quantex-Ray/Micro-× 7000 analytical spectrometer (Kevex Corp, Foster City, CA) as a means of analyzing the tissue for the detection and quantification of Gd-DTPA-dimeglumine. Using this technique, the lower border of detectability for Gd-DTPA-dimeglumine was 5–10 μmol/L concentrations.

Results

Macroscopic Examination

In the ten knees injected with Gd-DTPA dimeglumine, one exhibited a minimal amount of clear intra-articular fluid at 6 hours after injection. Another exhibited mild hyperemia on gross pathologic examination at 24 hours after injection. The remaining eight knees exhibited normal appearing synovium and articular cartilage without effusion. One of the seven knees with intra-articular saline solution exhibited a minimal amount of clear intra-articular fluid at 6 hours after injection, and another demonstrated mild hyperemia of the synovium at 24 hours after injection. Otherwise, findings in the synovium and cartilage were normal for the remaining injected knees as well as the noninjected joints.

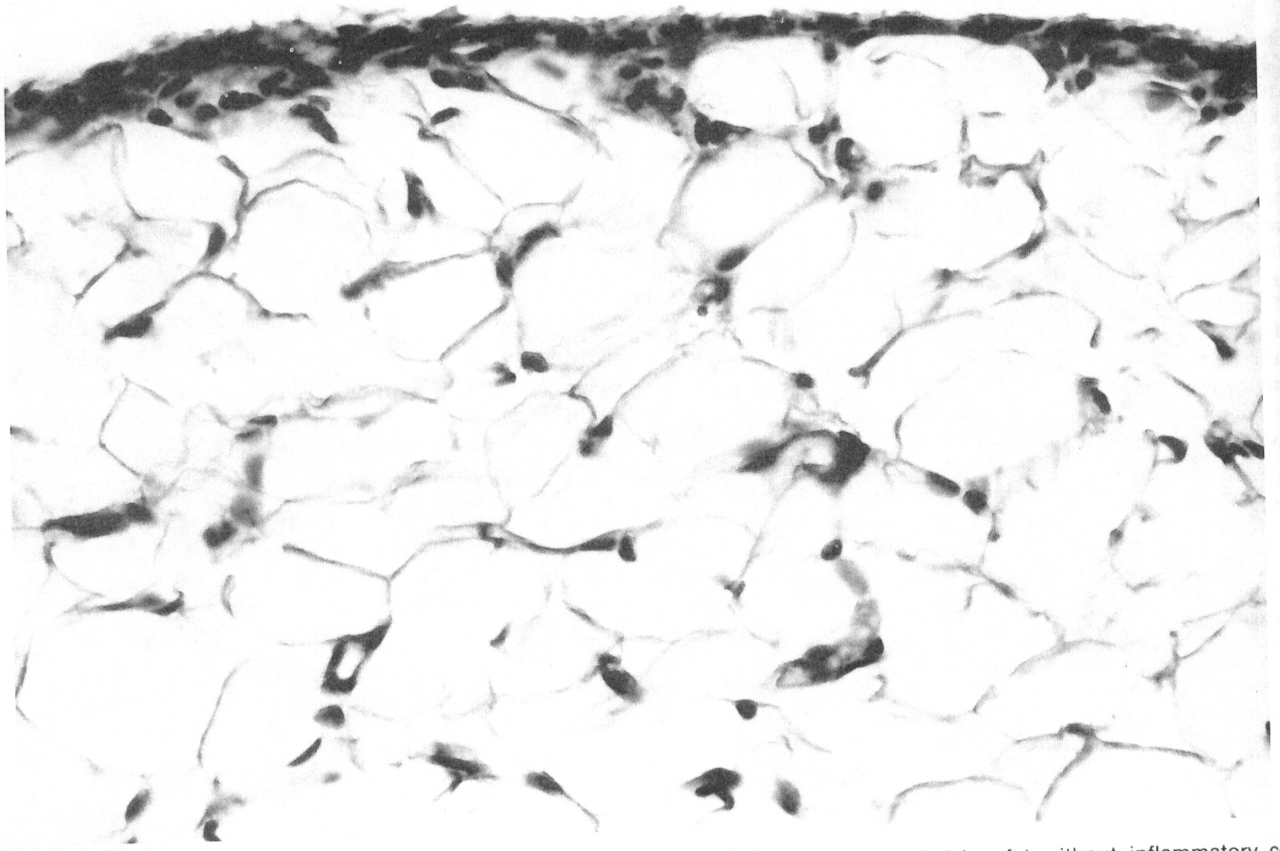

Fig. 1. Normal synovium showing synoviocytes at the top of the photograph with underlying fat without inflammatory cells (hematoxylin and eosin, original magnification × 100).

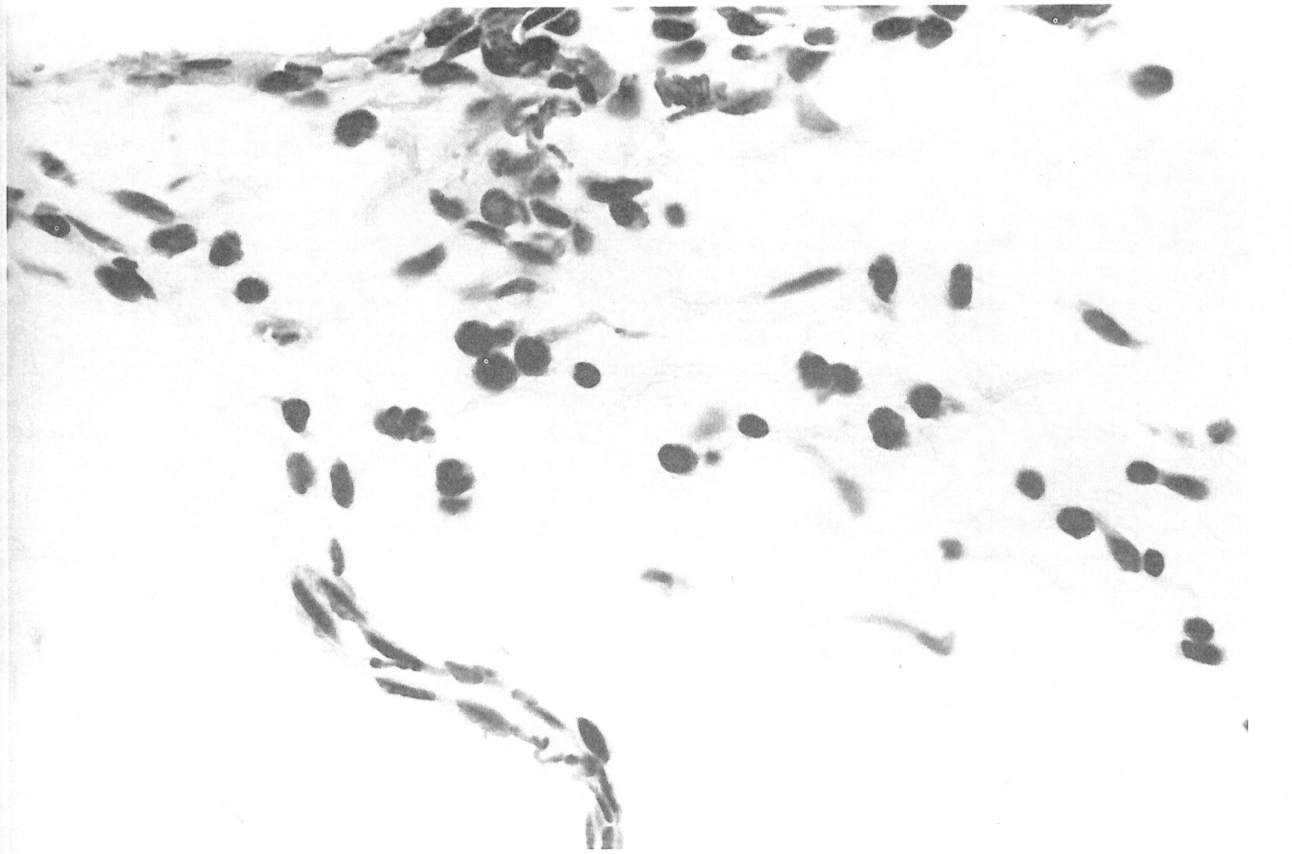

Fig. 2. Synovium showing few inflammatory cells consisting of plasma cells, lymphocytes, mast cells, histiocytes, and occasional polymorphonuclear leukocytes (neutrophils) under synovial lining (upper border of photograph). This was a small focus of inflammation. The rest of the synovium was essentially unremarkable and showed limited focus of hyperemia (hematoxylin and eosin, original magnification × 160).

Microscopic Examination

Three knees exhibited normal appearing synovium after intra-articular injection of Gd-DTPA-dimeglumine (Fig. 1). Minimal focal hyperplasia of the synovium was found in four kneess at 2, 6, and 24 hours and at eight days after Gd-DTPA-dimeglumine injection as well as in two knees at 2 hours and eight days after saline solution injection. Focal minimal to mild congestion of the synovium with dilated vessels was seen three times at 6 and 24 hours and eight days in the knees injected with saline solution. Minimal focal monomuclear cell infiltration with rare plasma cells beneath the surface synovial cells could be appreciated at 24 and 72 hours and at eight days in three knees injected with Gd-DTPA-dimeglumine and at 2 and 72 hours in two knees with intra-articular saline solution (Fig. 2). Focal subsynovial fibrosis was appreciated in all knees at the puncture site. The three knees that underwent puncture exclusively, manifested only mild focal synovial hyperplasia, vascular congestion, and minimal subsynovial polymorphonuclear cell infiltration (Fig. 3).

X-ray Fluorescent Spectroscopy

All knees injected with Gd-DTPA-dimeglumine demonstrated no evidence of the material in the synovium or articular cartilage.

Discussion

The biologic distribution and behavior of Gd-DTPA-dimeglumine in animals and humans after intravenous injection have been well established.[8–10] Gd-DTPA-dimeglumine is currently approved for intravenous injection in concentrations of up to 0.1 mmol/L/kg body weight. To improve the accuracy of MRI in the diagnosis of joint disorders, intra-articular injection of this material

has been proposed.[6,12] In a previous study, it was determined that a minimal concentration of 500 μmol/L Gd-DTPA-dimeglumine affords acceptable signal intensity contrast to articular cartilage.[7] The current investigation evaluated the potential effects of 500 μmol/L Gd-DTPA-dimeglumine on the synovial membrane and joint cartilage.

Macroscopically, there were no pathologic findings; specifically, edema and hyperemia of the synovium were absent. The histologic results revealed no definite difference between the minimal synovial reaction of 500 μmol/L Gd-DTPA-dimeglumine and saline solution. The mild cellular response and focal synovial hyperplasia are most likely a reaction to the trauma of the needle puncture and articular distension.[13] This is supported by the fact that three joints subjected only to needle puncture exhibited similar mild synovial infiltration by leukocytes as well as hyperplasia and fibrosis of the synovial membrane. Although Gd-DTPA-dimeglumine is a strongly hydrophilic substance with high osmolarity, this study indicated that the minimal synovial changes seen by microscopy did not correlate with osmolarity, because introduction of saline solution alone into joint cavities caused a similar response.

As shown in this investigation, Gd-DTPA-dimeglumine is resorbed by the synovium within a few hours and does not induce intra-articular effusion. Its resorption rate should be similar to that of iodinated contrast agents and chiefly determined by the molecular weight of the molecule.

Intravenous administration of Gd-DTPA-dimeglumine up to concentrations of 0.1 mmol/L/kg body weight has been proved safe in humans.[10,13] The concentration used in this study is 1:10 of that for intravenous administration. Therefore, the total amount of Gd-DTPA-dimeglumine necessary for MR arthrography of this articulation lies far beyond the established safety limit. The quantitative analysis of articular cartilage and synovium in this study indicated no evidence of Gd-DTPA-dimeglumine storage. The values for the control group were comparable to those of the knees injected with Gd-DTPA-dimeglumine. These results must be interpreted with caution, however, because

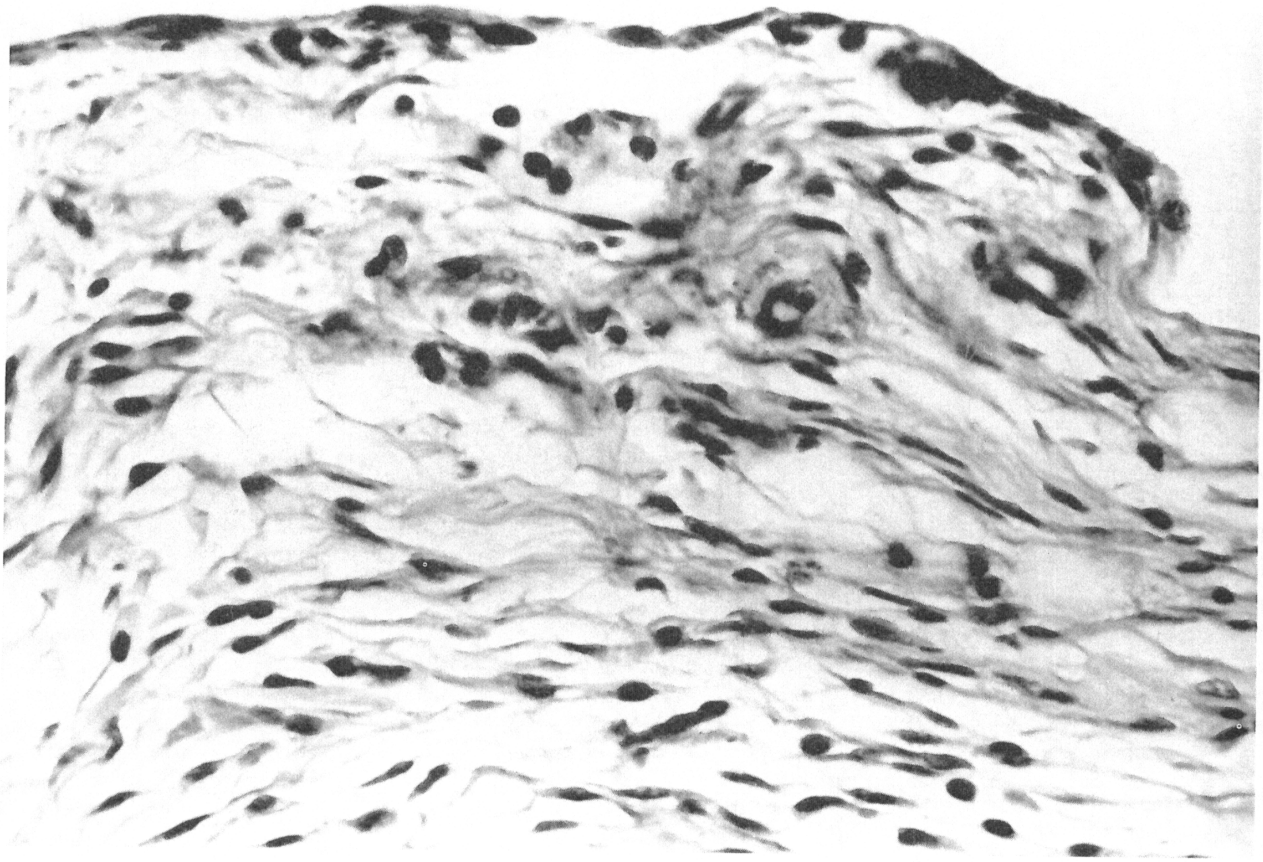

Fig. 3. Synovium showing focus of subsynoviocytic fibrosis and few inflammatory cells similar to Figure 2. Elsewhere there were multiple small foci of similar inflammatory cells under synovial lining as well as deeper within fat (hematoxylin and eosin, original magnification × 100).

x-ray fluorescent spectroscopy affords limited sensitivity in the detection of Gd-DTPA-dimeglumine concentrations below 10 μmol/L.

In summary, this investigation shows that there are no significant gross pathologic or histologic alterations in the synovial membrane resulting from the introduction of 500 μmol/L Gd-DTPA-dimeglumine into rabbit knees. In addition, no evidence for accumulation of this material in articular cartilage or synovium was found. These conclusions, however, need to be further verified before implementation in human subjects.

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