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Enhancement of Intervertebral Disks with Gadolinium Complexes: Comparison of an Ionic and a Nonionic Medium in an Animal Model

Michael A. Ibrahim, Victor M. Haughton, and James S. Hyde

PURPOSE: To compare MR contrast enhancement of intervertebral disk tissue after intravenous administration of equimolar doses of an ionic and of a nonionic gadolinium complex. **METHODS:** Contrast enhancement was measured on MR in lumbar intervertebral disks for 120 minutes after intravenous injection of gadoteridol or gadopentetate dimeglumine, 0.3 mmol/kg. MR studies were performed with each contrast medium in four rabbits. Contrast enhancement was measured in intervertebral disks as a function of time and contrast medium. **RESULTS:** With both contrast media, enhancement of normal intervertebral disks was detected. Enhancement of disks was significantly greater with gadoteridol than with gadopentetate dimeglumine. **CONCLUSION:** The enhancement of cartilage is influenced by the molecular structure of the gadolinium complex. The negative charge of gadopentetate dimeglumine may give it a slower rate of diffusion into disk cartilage than a nonionic complex.

Index terms: Contrast media, comparative studies; Contrast media, paramagnetic; Spine, intervertebral disks; Spine, magnetic resonance; Animal studies

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The clinical utility of contrast enhancement requires the selective or relatively greater enhancement of one of the tissues being compared (1). Commercially available water-soluble gadolinium chelates—gadoteridol, gadopentetate dimeglumine, and gadodiamide—produce similar results in many magnetic resonance (MR) applications (1–3) because they have similar relaxivities, volume of distribution, half life, and renal and plasma clearances. These contrast media differ in one important respect: gadopentetate dimeglumine is ionic, gadoteridol and gadodiamide are nonionic. One application in which the ionic and nonionic media may produce different results is in cartilage. Small nonionic molecules may diffuse into cartilage more rapidly than ionic ones (4). Enhancement of disk and joint cartilage after intravenous administration of gadopentetate dimeglumine has been reported (5). Per unit dose, disk fragments, in a model of recurrent disk herniation, enhanced to a significantly greater degree with gadoteridol than with gadopentetate dimeglumine (6). Therefore, we designed a study to test the hypothesis that in vivo after intravenous administration an ionic contrast medium diffuses more slowly into disk cartilage than does a nonionic medium.

Materials and Methods

Four adult female New Zealand White rabbits, 1 to 2 years of age, weighing 3.4 to 4.3 kg, underwent MR after the administration of gadopentetate dimeglumine (Magnevist injection, Berlex, Secaucus, NJ) or gadoteridol (ProHance, Bristol Meyer Squibb, Princeton, NJ) in a dose of 0.3 mmol/kg. Four MR studies were performed on each rabbit with 1 week between studies. Each animal received gadoteridol and gadopentetate dimeglumine twice. The sequence of contrast agent administration was randomized.

For MR imaging, the rabbits were sedated with a mixture of ketamine hydrochloride (Ketaset) (20 mg/mL) and xylazine hydrochloride (Rompun) (4 mg/mL) administered intramuscularly in a dose of 3.0 mL, with subsequent doses of 0.5 mL every 40 minutes. A 25-gauge needle was

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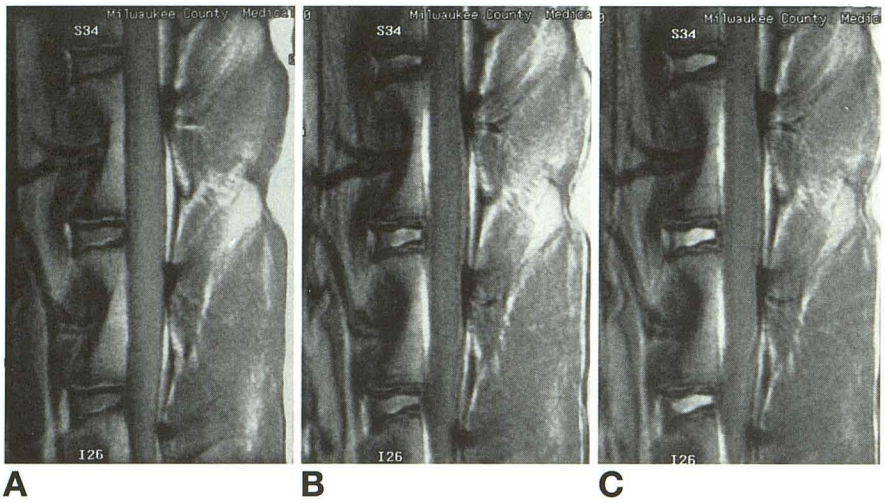

Fig 1. Sagittal images of a rabbit spine before injection (*A*), and at 30 (*B*) and 120 minutes (*C*) after injection of intravenous gadoteridol, 0.3 mmol/kg. The disk enhances first near the vertebral endplates and then throughout the disk.

inserted into the posterior auricular vein and flushed with heparin. Normal saline was administered intravenously at a rate of 40 mL/h. The rabbits were placed supine on a quadrature surface coil in a 1.5-T scanner. Sagittal images were obtained with a CPMG pulse sequence providing small fields of view (Jesmanowicz A, Hyde JS, Kneeland JB, "Pulse Sequences for Small Fields of View" [abstract], presented at the Seventh Annual Meeting of the Society of Magnetic Resonance, San Francisco, Calif, August 20-26, 1988). Imaging parameters were: 500/25/2 (repetition time/echo time/excitations); matrix, 256 × 256; field of view, 6 × 6 cm; section thickness, 3.0 mm; and no phase wrap. The contrast agent was injected through the venous cannula. Images were obtained at 2, 10, 20, 30, 45, 60, 90, and 120 minutes after injection of gadopentetate dimeglumine or gadoteridol. Signal intensities of the lumbar intervertebral disk closest to the center of the sensitive volume of the surface coil were measured in each image with the region-of-interest program on the system console and an elliptical cursor having an area of 2.0 mm^2. Contrast enhancement was calculated as the change in signal intensity from baseline divided by the baseline signal intensity. Contrast enhancement after gadopentetate dimeglumine and gadoteridol were compared and differences tested with Wilcoxon's rank sum test.

Results

Sixteen sets of precontrast and postcontrast images of the intervertebral disk with negligible movements of the animals were obtained in four rabbits. Contrast enhancement in disks was visible in the images obtained after intravenous contrast medium (Figs 1 and 2). Contrast enhancement was observed first near the inferior and superior endplates as a narrow band of increased signal intensity at 10 minutes in each animal. By 120 minutes, contrast enhancement was observed throughout the disk (Figs 1 and 2).

Enhancement was detected by means of cursor measurements. Contrast enhancement increased with time for both contrast agents (Fig 3). The maximum enhancement for gado-

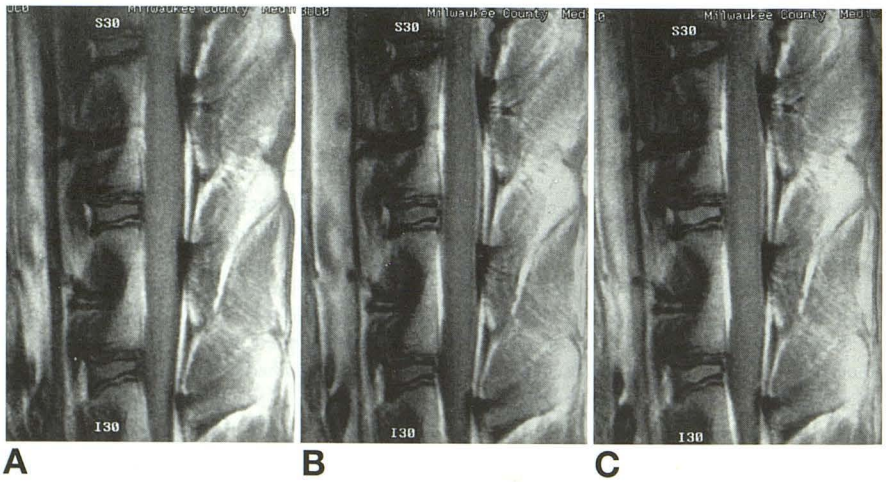

Fig 2. Sagittal images in the same rabbit before injection (*A*), and at 30 (*B*) and 120 minutes (*C*) after injection of intravenous gadopentetate dimeglumine. The disk enhances less with gadopentetate dimeglumine than with gadoteridol. Enhancement is detected near the vertebral endplates at 30 minutes and diffusely at 120 minutes.

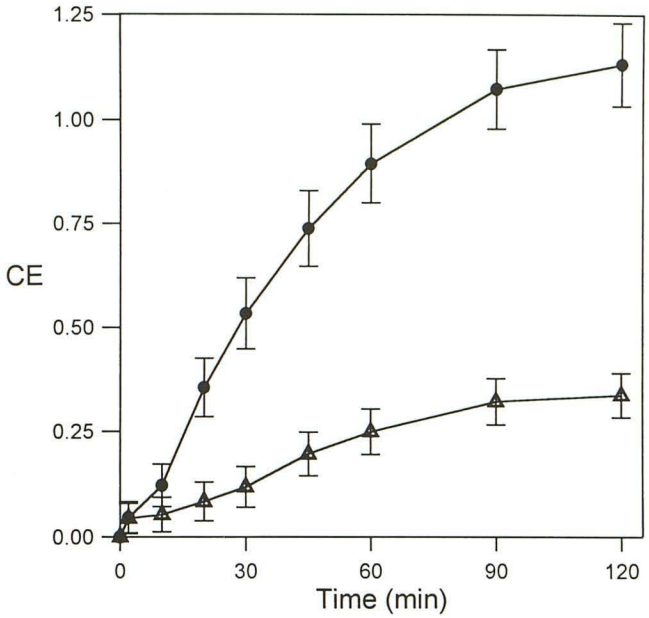

Fig 3. Average enhancement (CE) of normal rabbit intervertebral disks (and standard deviation) after injection of intravenous gadoteridol (*circles*) and gadopentetate dimeglumine (*triangles*).

pentetate dimeglumine and gadoteridol was 0.34 and 1.13, respectively. At 20 minutes after the injection of contrast medium, enhancement in the disk with gadoteridol was 2.6 to 5.3 times that of gadopentetate dimeglumine. The difference was significant at $P < .005$ as determined by a two-tailed Student's t test. At 120 minutes after the injection of contrast medium, the ratio of contrast enhancement for gadoteridol and gadopentetate dimeglumine was 2.4 to 4.2. This difference was also significant ($P < .005$).

Discussion

Small molecules like glucose and sulfate with molecular weights less than 1000 diffuse readily through the proteoglycan gel (7–11), which is the major constituent of cartilage in the nucleus pulposus and inner annulus fibrosus and in diarthrodial joints. Diffusion supplies the nutrients to and removes the waste material from the thousands of cells per cubic millimeter in the intervertebral disk. The rate of diffusion of solutes in cartilage is a function of molecular weight, charge of the contrast medium, fixed-charge density, and pore size in the matrix.

Cartilage, such as the fibrocartilage in the intervertebral disks, contains complex, high-molecular-weight polymers (proteoglycans) that are not free to diffuse. The sulfated glycosaminoglycans of the polymers provide a high concentration of anions that also are not free to diffuse. These fixed negative charges are electrostatically balanced by cations, which create a higher osmotic pressure in the disk than in surrounding tissues. Water is retained in the disk, against a pressure gradient, by the fixed negative charges. The fixed negative charges may hinder the diffusion into cartilage of the gadopentetate dimeglumine, which dissociates fully in solution into an anion and two meglumine cations. Gadoteridol, a neutral molecule, passes through the pores more readily.

Gadoteridol and gadopentetate dimeglumine differ also in formula weight (559 versus 938), relaxivity (3.7 versus 3.8 $mM^{-1}s^{-1}$), viscosity, osmolarity, molar conductivity, and type of chelate (linear versus macrocyclic) (3). The relative rate of diffusion, calculated on the basis of molecular weight, of gadopentetate dimeglumine and gadoteridol in solution may explain a small fraction of the difference in contrast enhancement observed between the two. The linear versus macrocyclic structure, relaxivity, and osmolarity likely do not explain large differences in diffusion.

The rabbit disk resembles the human disk in general structure (12). The rabbit intervertebral disk adjoins thin platelike epiphyses of the vertebrae, which lack the annular formation seen in humans. As in the human, the rabbit annulus is composed of concentric lamellae of fibrocartilage. The fixed negative charges associated with chondroitin and keratin sulfate in the proteoglycans retain water in the disk. In the rabbit disk, as in the human disk (13), the nucleus consists of 85% water. With a tear of the annulus fibrosus, nuclear degeneration ensues in rabbits as in humans. The variation in the structure of the nucleus with age is analogous to that of human intervertebral disks (12). The rabbit disks are avascular, as are human disks. The rabbit disk appears to have a low rate of metabolism, as does the human disk, nourished by diffusion or fluids from surrounding tissues, especially the epiphysis and vertebral bodies.

The study is based on a small number of observations in rabbits. Nonetheless, statistical significance was reached. At 20 to 120 minutes after injection of contrast media, the differences between disk enhancement for the two media were significant. We have not verified that rabbit disks have the same diffusion properties as human disks, but previous investigators have as-

sumed it was similar on the basis of similarities in the proteoglycans (7, 8).

The study suggests that in differentiating recurrent herniated disk from scar, gadopentetate dimeglumine and gadoteridol may have significantly different results. Gadopentetate dimeglumine may diffuse more slowly than gadoteridol into disk fragments. In previously laminectomized patients, gadopentetate dimeglumine likely will produce better contrast between scar tissue and a disk fragment. This hypothesis can be tested in an experimental model of recurrent herniated disk (5) or in a clinical study. On the other hand, if the objective of giving contrast medium is to achieve enhancement in the cartilage, gadoteridol likely will produce better enhancement than gadopentetate dimeglumine. Measurement of enhancement in the intervertebral disk may provide a measure of diffusion into the disk (7). Impaired diffusion of solutes into the disk has been thought to characterize early disk degeneration (7).

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