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M A Ibrahim, V M Haughton and J S Hyde

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Effect of Disk Maturation on Diffusion of Low-Molecular-Weight Gadolinium Complexes: An Experimental Study in Rabbits

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

PURPOSE: To measure the rate of enhancement in immature intervertebral disks in comparison with that of mature disks after intravenous administration of gadolinium-containing contrast media. **METHODS:** Four rabbits were imaged with MR for 120 minutes after the injection of gadopentetate dimeglumine, gadoteridol, or gadodiamide. Contrast enhancement was measured in the lumbar intervertebral disks on each image. The rate and magnitude of enhancement in the immature and mature disks were compared. **RESULTS:** Contrast enhancement was detected in intervertebral disks with all three contrast media. Enhancement was significantly greater in immature than in mature animals. **CONCLUSION:** Greater enhancement in immature disks is consistent with a lower concentration of fixed negative charges in the glycosaminoglycans of the disk.

Index terms: Spine, intervertebral disks; Spine, magnetic resonance; Magnetic resonance, contrast enhancement; Animal studies

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Low-molecular-weight molecules such as oxygen, sulfate, and gadolinium chelates diffuse into the intervertebral disk (1–5). Because the gadolinium chelates diffuse into the disk, contrast enhancement of the disk is detected in magnetic resonance (MR) imaging if doses of contrast medium and delay between injection and imaging are sufficient (4, 5). The rate of diffusion through the disk is related to the charge on the molecule, the molecular weight, and other factors. The ionic contrast medium gadopentetate dimeglumine diffuses more slowly through cartilage than do the nonionic media gadoteridol and gadodiamide, presumably because of the fixed negative charges in cartilage that impede the diffusion of charged particles (4). Hypothetically, the composition of the disk, which is altered by maturation and degeneration, affects the diffusion of the gadolinium chelates through the matrix. To test this hypothesis, we measured the diffusion of gadolinium chelates through immature disks and compared the rates with those in mature disks.

Methods

Four immature female New Zealand White rabbits, 2.2 to 2.3 kg in weight, underwent MR studies with three contrast media. Each rabbit had MR with gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Seacacus, NJ), gadoteridol (ProHance, Bristol-Meyer Squibb, Princeton, NJ), and gadodiamide (Omniscan, Sanofi-Winthrop, New York, NY). In each rabbit, each contrast medium was administered in a dose of 0.3 mmol/kg, with 1 week between studies and with the order or administration randomized.

For MR, animals were sedated with 2 mL of a mixture of 20 mg/mL ketamine hydrochloride (Ketaset, Aveco, Fort Dodge, Iowa) and 2 mg/mL xylazine hydrochloride (Rompun, Mobay, Shawnee, Kan) intramuscularly and supplementary doses of 0.5 mL intravenously every 40 minutes. The posterior auricular vein was cannulated with a 25-gauge needle, and 0.9% saline was administered intravenously at a rate of 40 mL/h. The rabbits were positioned supine on a quadrature surface coil (10) in a 1.5-T imager. Locater images and then sagittal images through the lumbar spine were obtained with a spin-echo pulse sequence providing small fields of view (500/25/2 [repetition time/echo time/excitations], 6-cm field of view, 3-mm section thickness) (Jesmanowicz A, Hyde JS,

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From the Biophysics Research Institute, Department of Radiology, Medical College of Wisconsin, Milwaukee.

Address reprint requests to Victor M. Haughton, MD, Department of Radiology, Medical College of Wisconsin, Doyne Clinic, 8700 W Wisconsin Ave, Milwaukee, WI 53226.

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Kneeland JB, "Pulse Sequences for Small Fields of View" [abstract], presented at the Seventh Annual Meeting of the Society of Magnetic Resonance, August 20–26, 1988, San Francisco, Calif) and no phase wrap. The contrast medium was injected as a bolus through the venous cannula. Images were repeated at 2, 10, 20, 30, 45, 60, 90, and 120 minutes and inspected for evidence of enhancement. Signal intensity in the midline section in the intervertebral disks closest to the coil was measured with an elliptical cursor 2 mm^2 in area. Contrast enhancement was calculated as the change in signal intensity from the baseline divided by the baseline signal intensity. Contrast enhancement, plotted as a function of time for each contrast medium as in a previous study (5), was compared to the plots from the previous study in which gadopentetate dimeglumine or gadoteridol were administered intravenously to 4 adult New Zealand white rabbits, 3.4 to 4.3 kg in weight (5). The same experimental protocol was used in this and in the previous study, except that gadodiamide was not used. The contrast enhancement measurements in both mature and immature disks were fitted to a function:

$$CE(t) = K[1 - \exp(-\alpha t)]$$

in which K represents an enhancement coefficient; t, the time after injection; and α, a rate constant. The values of K and α were calculated for each data set. The K and α values were averaged for mature and immature disks and contrast medium. The K and α values were compared for the two contrast media and for the mature and immature disk.

Differences between groups were tested for significance by means of the one-tailed t test.

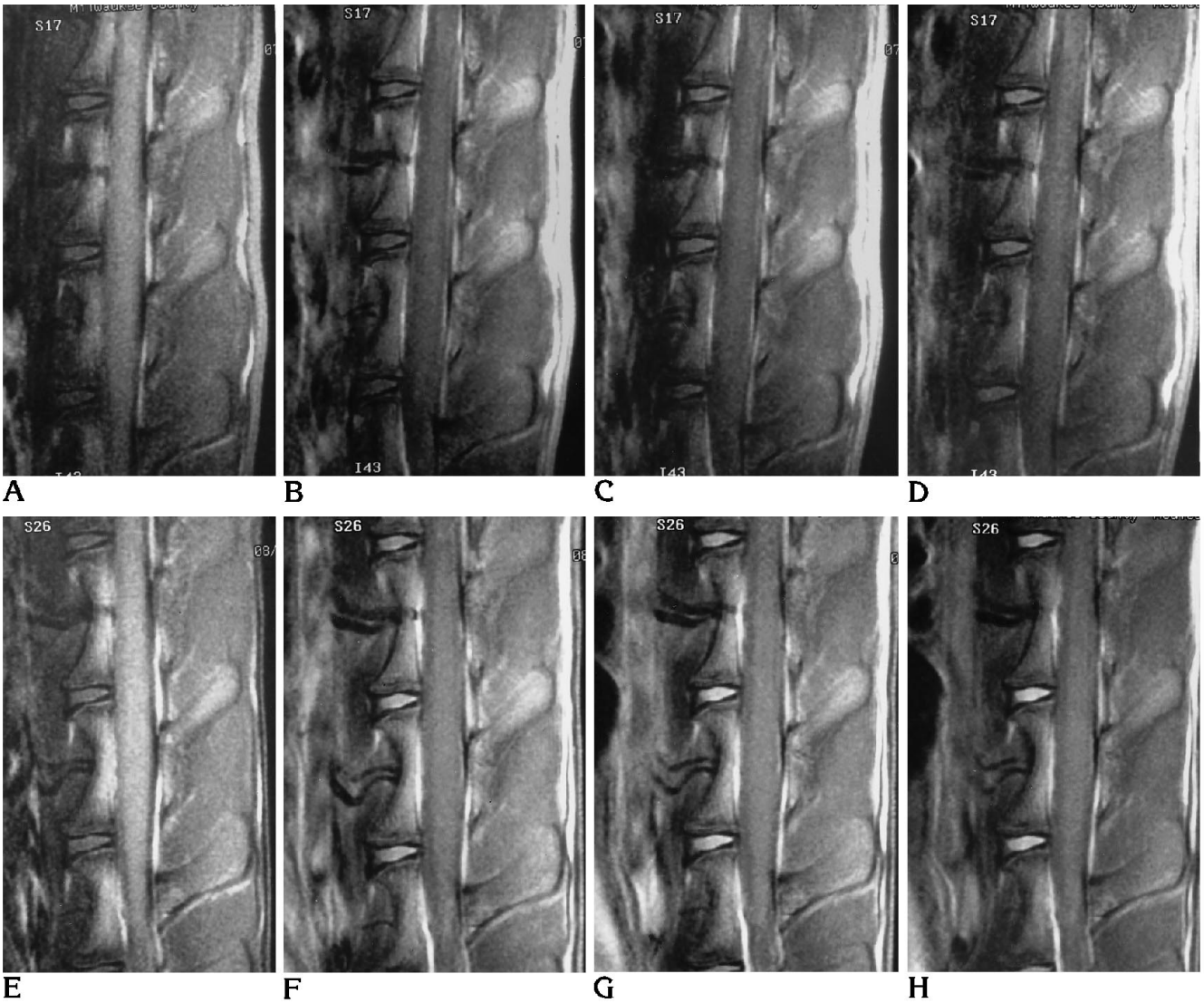

Fig 1. Sagittal images of the immature rabbit lumbar spine before (*A*) and after (*B*, 30 minutes; *C*, 60 minutes; *D*, 120 minutes) injection of gadodiamide and before (*E*) and after (*F*, 30 minutes; *G*, 60 minutes; *H*, 120 minutes) injection of gadopentetate dimeglumine. Note that intervertebral disks enhance more conspicuously after injection of gadodiamide.

Results

Each of the 12 MR studies was technically adequate for measuring contrast enhancement. Contrast enhancement was evident in the intervertebral disks in each sequence of images, usually by 20 minutes. Enhancement was conspicuously greater with the nonionic media (gadoteridol, gadodiamide) than with the ionic medium (gadopentetate dimeglumine) (Fig 1). Contrast enhancement in the intervertebral disk in the four immature rabbits is plotted in Figure 2A, and contrast enhancement in four adult rabbits studied similarly is plotted in Figure 2B. The contrast enhancement coefficients and rate constants for the three contrast media, together with the same constants for mature rabbits, are listed in the Table and plotted in Figure 3.

Differences between Immature and Mature Intervertebral Disks

The immature rabbit disks had greater enhancement coefficients and rate constants than mature rabbit disks, especially when the ionic contrast medium was used. The enhancement coefficient for immature rabbits with the ionic medium was 0.73 and for mature rabbits with the same medium was 0.48. The difference was significant at the .01 level. For the nonionic media, the rate constants averaged 1.45 to 1.50 for the immature disks and 1.42 for the mature disks. The differences were not significant. The rate constant for the ionic contrast medium was 0.037 in the immature disks and 0.012 in the mature disks, and the difference was significant at the .01 level. For the nonionic media, the rate constant was 0.034 for immature disks and 0.017 for mature disks, a difference that was significant at the .02 level.

Differences between Media

The enhancement coefficients for the nonionic media were greater than the same constants for the ionic medium in the immature disks and in the mature disks. Enhancement coefficients were significantly greater ($P < .001$) for gadoteridol (average, 1.5) or for gadodiamide (average, 1.48) than for gadopentetate dimeglumine (average, 0.73) in immature rabbit disks. In mature disks, the enhancement coefficients (average, 1.42) also were significantly ($P < .01$) greater than for the ionic medium (average, 0.48). The rate constants did not differ significantly between media. The rate constant for the nonionic media in immature disks was 0.03 compared with 0.04 with the ionic medium ($P = .4$). In the mature disks, the rate constant was 0.02 for the nonionic medium and 0.01 for the ionic medium ($P = .1$).

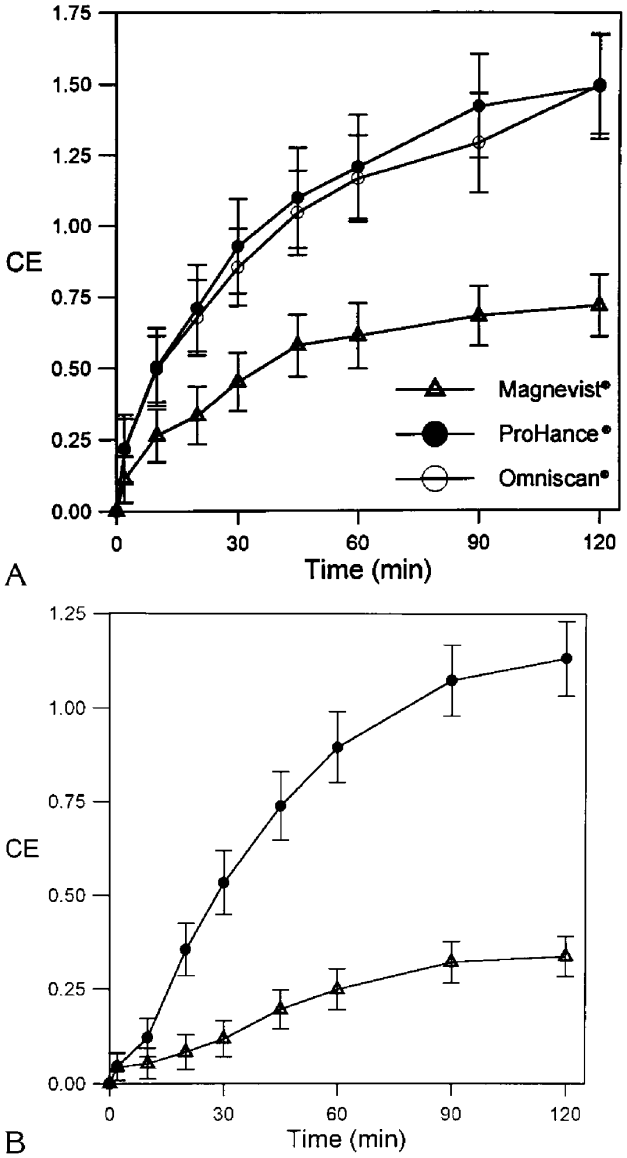

Fig 2. Contrast enhancement in rabbit intervertebral disks after injection of ionic (gadopentetate dimeglumine [Magnevist]) and nonionic (gadodiamide [Omniscan] and gadoteridol [ProHance]). The average and standard deviations of contrast enhancement in four immature rabbits (*A*) and four mature rabbits (*B*) are plotted as a function of time after injection. (Data for B are from reference 5.)

Enhancement coefficients (K) and rate constants (α) for ionic and nonionic media in immature and mature disks

	Rabbit	Immature		Mature	
		K	α	K	α
Gadopentetate dimeglumine	1	0.78	0.025	0.43	0.012
	2	0.65	0.053	0.38	0.015
	3	0.77	0.044	0.44	0.010
	4	0.70	0.026	0.68	0.010
	Average	0.73	0.037	0.48	0.012
	SD	0.053	0.012	0.12	0.0020
Gadoteridol	1	1.51	0.018	1.58	0.017
	2	1.54	0.037	1.45	0.013
	3	1.60	0.040	1.43	0.010
	4	1.36	0.040	1.22	0.027
	Average	1.50	0.034	1.42	0.017
	SD	0.089	0.010	0.13	0.0065
Gadodiamide	1	1.17	0.029		
	2	1.43	0.021		
	3	1.61	0.037		
	4	1.58	0.038		
	Average	1.45	0.031		
	SD	0.17	0.007		

Discussion

Contrast enhancement in the intervertebral disk can be described in terms of an enhancement coefficient and a rate constant. After the injection of a bolus of the gadolinium complex, enhancement in the intervertebral disk asymptotically approaches a plateau, which we have defined as the *enhancement coefficient*. The enhancement coefficient is a measure of the maximal enhancement reached after an injection of contrast medium. For different contrast media or different disks, the enhancement coefficient may vary. For example, the coefficient is greater for nonionic than for ionic media and greater for immature than for mature disks. Intervertebral disk enhancement approaches the plateau at different rates, depending on the composition of the disk and of the molecule. The rate constant is a measure of the rate at which the disk increases in enhancement. The rate constants are greater in immature than in mature disks. The enhancement coefficient and the rate constant can be used to describe the enhancement of the disk. For example, the enhancement of the disk at any time after injection is calculated from the enhancement coefficients and rate constants. The rate constants in this study were significantly greater for immature than for mature disks. The enhancement coefficients were significantly greater for nonionic than for ionic media.

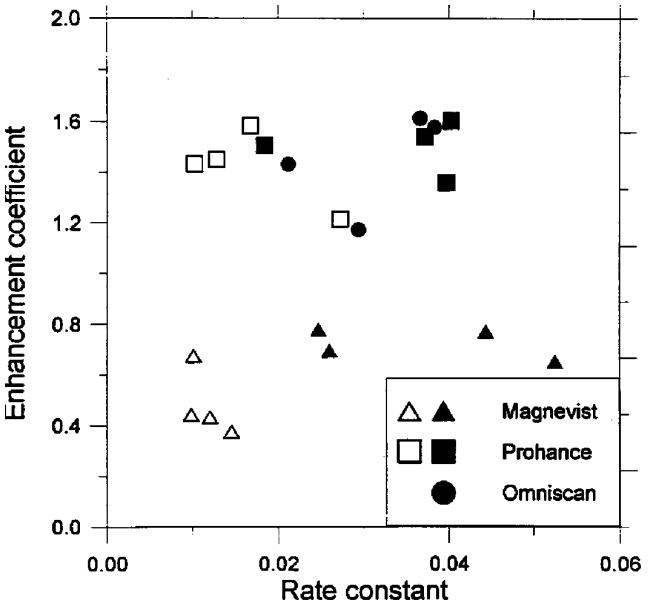

Fig 3. Plot of enhancement coefficients versus rate constants for immature and mature rabbit disks with gadopentetate dimeglumine (Magnevist), gadoteridol (ProHance), and gadodiamide (Omniscan). *Filled symbols* represent data for immature rabbit disks and *open symbols* for mature rabbit disks.

The greater enhancement coefficients and rate constants (with ionic medium) in immature rabbit disks compared with mature rabbit disks indicate more rapid diffusion. The greater rate of enhancement may be explained by differences in the end plates or by differences in the composition of the disk. The contact between

the disk and blood vessels in the end plate is greater in immature disks than in adult disks (11, 12). The younger end plates also are more permeable (13). Maturation of the disk affects the enhancement coefficient and rate constant of gadopentetate dimeglumine differently than those of gadoteridol. This difference could be explained by an increase in the fixed negative charges in cartilage with maturation. Fixed negative charges hinder the diffusion of negatively charged particles more than uncharged molecules. Radioisotope studies support the conclusion that ionic particles diffuse differently than nonionic molecules (1, 3).

This study was designed as a pilot for more-extensive studies on the effect of disk composition on diffusion of contrast media. A limited number of animals was therefore used. The study was terminated at 120 minutes, when enhancement was near maximal according to unpublished studies (Ibrahim MA, *Mathematical and Pharmacokinetic Modelling of MRI Contrast Agent Transport into the Intervertebral Disks*, Milwaukee: Medical College of Wisconsin; 1994, dissertation.) The composition of disks was not studied in this experiment. However, other investigators have shown that in the young rabbit disks, proteoglycan concentrations are changing (14).

After intravenous injection of contrast medium, diffusion of contrast medium into the disk can be characterized by an enhancement and rate constant. These constants may be affected by changes in the vertebral end plates or the composition of the disk. Changes in diffusion into the disk, according to one theory, is an early marker of disk degeneration. This study suggests that MR imaging with intravenous gadolinium chelates may be used to test this hypothesis.

In summary, enhancement in intervertebral disks is a function of the composition of the disk and of the contrast medium. Contrast enhancement diminishes as the disk matures. Maturation of the disk is accompanied by a slowing of the enhancement coefficient and rate constant for enhancement. The enhancement coefficients for both immature and mature disks are greater for nonionic than for ionic paramagnetic media.

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