THE CHANGES IN THE INTERVERTEBRAL DISC AFTER CHEMONUCLEOLYSIS DEMONSTRATED BY MAGNETIC RESONANCE IMAGING

M. J. GIBSON, J. BUCKLEY, R. C. MULHOLLAND, B. S. WORTHINGTON

From the Spinal Research Unit, Harlow Wood Orthopaedic Hospital, and the Department of Radiology, University Hospital, Nottingham

Magnetic resonance imaging (MRI) of the spine produces images which reflect the chemical composition of the intervertebral disc. We have conducted a prospective study of the serial changes in the MRI appearance of the intervertebral disc after chemonucleolysis with the enzyme chymopapain.

Fourteen patients were studied after single-level chemonucleolysis and the results compared with a control group of 17 discs in six patients who had diagnostic discography without enzyme insertion. A consistent pattern of gradual loss of signal from the nucleus pulposus culminating in complete loss of nuclear signal was seen in all cases after chemonucleolysis. Chymopapain therefore produced MRI changes analogous with premature gross disc degeneration. The rate at which this occurred varied; complete loss of signal took at least six weeks.

Transitory minor end-plate changes were present in five patients, probably representing a mild chemical discitis. No similar changes were seen in the discography group.

Chemical dissolution of the nucleus pulposus of the intervertebral disc by the enzyme chymopapain was first described 22 years ago (Smith 1964). The efficacy of chymopapain over placebo has been proved in double-blind randomised studies (Javid et al. 1983; Fraser 1984) and the technique is now an established treatment for sciatica due to intervertebral disc protrusion (McCulloch and Macnab 1983; Wiltse 1983). However, the exact mechanism of action of this proteolytic enzyme in vivo is still not known. In vitro it has been shown to act by hydrolysis of the non-collagen ground substance of the nucleus pulposus (Stern 1969; Garvin, Jennings and Stern 1977). The chymopapain binds to the acid mucopolysaccharides (Stern and Smith 1967) and splits the proteoglycans which are normally responsible for maintaining the high water content of the nucleus pulposus (Puschel 1930; Gower and Pedrini 1969; Hirsch et al. 1953; Naylor and Horton 1955; Lipson and Muir 1981). Chymopapain should therefore produce a secondary desiccation of the nucleus pulposus.

Magnetic resonance imaging (MRI) is a new technique for demonstrating spinal pathology. When the spin echo imaging technique is used a high signal is produced by the nucleus pulposus. This probably reflects its high water content in a normal intervertebral disc (Han, Benson and Yoon 1984; Modic et al. 1984). Changes in the chemical composition of the nucleus pulposus affecting the water content after chemonucleolysis should be shown by MRI. Two recent publications (Chafetz et al. 1983; Modic et al. 1984) have noted that MRI scans after chymopapain injection have shown disc space narrowing and loss of signal from the nucleus pulposus.

This study assesses the serial changes in the signal from the nucleus pulposus in the first three months after chemonucleolysis.

MATERIAL AND METHODS

Fourteen patients with acute sciatica secondary to disc protrusion were studied. The diagnosis was made clinically and confirmed by radiculography and in some cases with computerised axial tomography. The group consisted of seven men and seven women with an age range from 14 to 40 years (mean 24 years).

Chymopapain was injected at a total of 14 levels, and in all cases the chemonucleolysis was performed by the same operator to minimise variation in technique. The needles were inserted via the posterolateral approach (McCulloch and Waddell 1978). Needle position was confirmed with 1 ml Niopam 300 and the dose of chymopapain given was 10 mg.
The MRI scans were all taken using the same machine, a 0.15 tesla-resistive magnet unit (Picker International). The imaging sequences employed were either spin echo \( T_R \) 2000 ms \( T_I \) 80 ms or \( T_R \) 2000 ms/\( T_I \) 40 ms producing \( T_2 \)-weighted images, or using an inversion recovery sequence when \( T_1 \)-weighted images were required. Scans were taken in the sagittal and parasagittal planes across the disc. The slice thickness of each section was 1 cm.

All patients were scanned before injection and at least twice after chemonucleolysis. The timing of the scans varied and is shown in Table 1. The first scan was within the first two weeks after the injection in all cases. The second scan was between one and two months after injection. Eight of the 14 patients were re-scanned for a third time three to six months after injection.

A control group of six patients, who were having multiple level discography at a total of 17 discs, without insertion of chymopapain, were also scanned. Scans were performed before discography and at similar intervals to the chemonucleolysis group in the three months after the injection, so that the effects of intradiscal injection on the nuclear signal could be assessed. In an earlier study (Gibson et al. 1986) comparing discography and MRI, no gross change in the nuclear signal was seen after discography.

RESULTS

The pre-treatment scans. The nuclear signal from the protruded disc was abnormal in all cases. The disc protrusion was demonstrated in 12 of the 14 patients. In the other two patients the nuclear signal was reduced, producing an abnormality similar to that seen in early to moderate disc degeneration. In 10 patients there was an abnormal signal from more than one disc. When this was...
Table I. Results of the serial MRI scans in 14 patients treated by chemonucleolysis

<table>
<thead>
<tr>
<th>Age of patient</th>
<th>Number of abnormal discs</th>
<th>Protrusion demonstrated</th>
<th>Timing (days)</th>
<th>Nuclear signal</th>
<th>End-plate change</th>
<th>Timing (weeks)</th>
<th>Nuclear signal</th>
<th>Timing (weeks)</th>
<th>Nuclear signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>No change</td>
<td>None</td>
<td>6</td>
<td>Complete loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>No</td>
<td>7</td>
<td>No change</td>
<td>None</td>
<td>8</td>
<td>Complete loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>Minor reduction</td>
<td>None</td>
<td>6</td>
<td>Signal reduced</td>
<td>14</td>
<td>Complete loss</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>No change</td>
<td>None</td>
<td>6</td>
<td>Complete loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36*</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>No change</td>
<td>Minor</td>
<td>6</td>
<td>Marked reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>1</td>
<td>Yes</td>
<td>14</td>
<td>Moderate reduction</td>
<td>None</td>
<td>8</td>
<td>Marked reduction</td>
<td>26</td>
<td>Complete loss</td>
</tr>
<tr>
<td>39</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>No change</td>
<td>None</td>
<td>4</td>
<td>Signal reduced</td>
<td>20</td>
<td>Complete loss</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>No</td>
<td>7</td>
<td>Moderate reduction</td>
<td>Definite</td>
<td>4</td>
<td>Marked reduction</td>
<td>32</td>
<td>Complete loss</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>Yes</td>
<td>14</td>
<td>Moderate reduction</td>
<td>None</td>
<td>8</td>
<td>Marked reduction</td>
<td>14</td>
<td>Complete loss</td>
</tr>
<tr>
<td>17*</td>
<td>3</td>
<td>Yes</td>
<td>6</td>
<td>Minor reduction</td>
<td>Minor</td>
<td>8</td>
<td>Signal reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>Yes</td>
<td>2</td>
<td>No change</td>
<td>None</td>
<td>4</td>
<td>Marked reduction</td>
<td>30</td>
<td>Complete loss</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>Yes</td>
<td>14</td>
<td>Marked reduction</td>
<td>Minor</td>
<td>8</td>
<td>Complete loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23*</td>
<td>1</td>
<td>Yes</td>
<td>8</td>
<td>Minor reduction</td>
<td>None</td>
<td>6</td>
<td>Marked reduction</td>
<td>24</td>
<td>Complete loss</td>
</tr>
<tr>
<td>23</td>
<td>2</td>
<td>Yes</td>
<td>11</td>
<td>Minor reduction</td>
<td>Definite</td>
<td>8</td>
<td>Marked reduction</td>
<td>22</td>
<td>Complete loss</td>
</tr>
</tbody>
</table>

* Chymopapain failures, operated upon after the second post-treatment scan

present it was not possible from the MRI scan to localise the level causing symptoms. Two patients had three levels of abnormality, eight had two levels (Fig. 1) and in only four was there a single abnormal disc.

First post-treatment scan. The timing of this scan varied between 2 and 14 days after injection. The results are shown on Table I.

The signal from the nucleus pulposus on these scans showed no significant change in six patients. In four of the eight patients in whom the signal was reduced, the degree of reduction was minor and significant reduction in signal was seen in only four cases. These were patients in whom the scans were performed later, more than a week after injection.

Minor changes in the signal from the vertebral end-plates on either side of the disc were present at a single scan in five patients. They were seen between five days and two weeks. They were never present on the second post-treatment scan. The presence of these end-plate changes did not correlate with the clinical course; they were not associated with any obvious increase in back pain after treatment.

Second post-treatment scan. This scan showed continued regression of the signal from the nucleus, although the degree of regression varied between patients. In four patients the signal had completely disappeared, in seven patients it was markedly reduced but still faintly present while in the other three the signal was reduced but was still clearly visible. In all cases the regression was accompanied by narrowing of the disc space; the space was at its narrowest when the nuclear signal had disappeared.

Third post-treatment scan. A third scan was performed on eight patients, the 10 in whom the nuclear signal had not disappeared on the second post-treatment scan but excluding the two in whom chymopapain had failed who had then been operated upon. On this final scan the signal from the nucleus pulposus had completely disappeared in all cases (Figs 2 to 4).

When a signal from a protruded fragment was demonstrated, it appeared to regress over the same time course as the rest of the nuclear signal.

Correlation with clinical results

Chemonucleolysis failed in three patients: two were designated as failures because the sciatica had not resolved by two months after injection, while a third patient developed a recurrence of sciatica more than three months after treatment and was also graded as a failure; all three patients to varying degrees showed an initial response to treatment followed by a recurrence of symptoms, and surgical decompression was performed in these cases. In the other 11 patients the chemonucleolysis produced satisfactory results. The failures showed similar reduction in the signal both from the nucleus and the protruded fragment, as was seen in the successes.

In the patients in whom the chemonucleolysis was successful there was some correlation between the rate of signal regression and the speed of clinical response. Those patients who improved slowly after the chemonucleolysis tended to take longer for nuclear signal regression on MRI. However, in most cases the symptoms had improved or disappeared before the maximal
Changes were demonstrated by MRI in the signal from the nucleus.

Results in the control group
In the six control patients, 17 discs were demonstrated discographically. Of these, nine were normal both on the initial MRI scan and the discograms. These discs, when rescaned up to three months after discography, showed no evidence of any change in signal and remained completely normal; there was thus no evidence that the discography had produced significant damage to the disc.

The other eight discs demonstrated by both techniques produced abnormal signals on the first scan. At these levels the signal also remained unchanged, suggesting that the discography had not further damaged the already abnormal disc.

Discussion
MRI is particularly appropriate to the study of the changes in the intervertebral disc after chemonucleolysis because the nuclear signal reflects the chemical composition of the nucleus. Thus any change in the nuclear signal after chemonucleolysis provides information both on the nature of the chemical change produced by the enzyme and the rate at which it occurs.

In this study a consistent pattern of gradual loss of nuclear signal, culminating in a complete loss, was shown in all cases. The rate at which the signal regressed varied, but complete loss of signal took at least six weeks. The end-result of enzyme action was a total loss of nuclear signal which gave the same MRI appearance as was seen in gross disc degeneration. This parallels the biochemical findings of Stern (1969), who noted that chymopapain produced biochemical changes similar to premature degeneration of the nucleus pulposus.

The loss of nuclear signal supports the idea that the enzyme acts by breaking down the proteoglycans in the nucleus with a secondary loss of water from the nucleus pulposus. This regression in the signal occurs over approximately the same time span as that for disc regression shown by computerised axial tomography (Konings, Williams and Deutman 1984; Brown et al. 1985; Gentry et al. 1985), and for maximal disc space narrowing as shown by plain radiography (Bitz and Ford 1977).

An important observation was the time taken for the changes in the nuclear signal to become apparent. There was little change in the first week and complete loss of signal took at least six weeks. This was surprising as the enzyme would be expected to act much more rapidly. In-vitro studies by Stern and Smith (1967) have shown that the enzyme binds almost immediately to the substrate and that enzyme action is complete in six hours. This speed of action has been used to explain the reflux of milky material that may occur at the time of injection. Clinical experience has shown that the response to treatment, in terms of loss of leg pain, often occurs within a few hours or days, implying that a change within the disc has occurred much more quickly than those demonstrated by MRI in this series.

It has been suggested that the enzyme acts by altering the physical characteristics of the herniated nuclear fragment "from concrete to cotton wool" (McCulloch and Macnab 1983). This is unlikely because both the physical characteristics of the nucleus pulposus material and the high MRI signal from it are due to the high water content of the tissue. In this study no rapid changes in the signal from either the nucleus pulposus or the protruded fragment were shown, so it seems unlikely that the consistency of the disc fragment was changed rapidly. Our findings in this respect agree with evidence from in-vivo animal experiments on the mechanism of action of the enzyme. Krempen, Minig and Smith (1975) noted no gross change in an extruded disc fragment in the first two weeks after injection of chymopapain. Loss of water from the herniated fragment may be the mechanism by which the enzyme produces its effect in those patients in whom the loss of symptoms occurs more slowly.

When the protruded fragment could be identified it appeared to regress over the same time course as the nuclear signal, so that by six weeks or two months after injection the signal had virtually disappeared. Interestingly, even after the signal from the nuclear fragment had gone there was often still quite marked annular bulging present, which could be seen indenting the epidural fat and thecal sac on T2-weighted images. This is not surprising, since chymopapain has no significant effect on the annulus and annular bulging is likely as the disc space narrows.

Patchy reduction in the signal from the vertebral end-plate regions adjacent to the disc was present in five patients (Fig. 5). Similar end-plate changes have been
previously reported in a single patient after chemo-
nucleolysis by Modic et al. (1984), although they found
an increased signal from the vertebral end-plate using a
T2-weighted sequence. On the T1-weighted inversion
recovery sequence end-plate change was shown as a
reduction in the signal from it. Recent use of the short
tau inversion recovery (STIR) sequence (Bydder and
Young 1985) suggests that it may be of particular value
in the demonstration of end-plate change. It produces
images with an increased signal from the end-plates
similar to that seen on a T2-weighted image. Since the
changes were transitory in all cases they may well have
occurred in a more minor form in some or all of the other
cases. This pattern of reduction in signal on T1-weighted
images, with increased signal on T2-weighted images,
suggests that a mild “chemical discitis” may have been
present. However, in this small series, these changes were
not associated with any increase in back pain after treat-
ment and appeared to be unrelated to the clinical course.

This study underlined the present limitations of low
field strength (0.15 tesla) MRI in the demonstration of
disc herniation. In the sagittal plane the signal from
herniated discs was never normal, but the abnormality
was sometimes non-specific – the same as is seen in early
disc degeneration. This change in nuclear signal after
disc herniation is probably related to chemical changes in
the nucleus, more specifically the loss of water from the
nucleus pulposus, since a 10% fall in the nuclear water
content has been shown to occur within two hours of disc
herniation (Hendry 1958).

Even when the disc protrusion could be identified it
could not be precisely localised; this would require better
spatial resolution, particularly in the transverse plane.
Recent papers (Edelman et al. 1985; Modic 1985) have
suggested that with the use of higher field strengths
(greater than 0.5 tesla) with surface coils, images can now
be produced which are comparable with computerised
tomography and capable of localising the disc herniation.

REFERENCES

Bitz DM, Ford LT. An evaluation of narrowing following intradiskal

Brown BM, Stark EH, Dion G, Ono H. Computed tomography
and chymopapain chemonucleolysis: preliminary findings. AJR 1985;
144:667-70.

Bydder GM, Young IR. MR imaging: clinical use of the inversion re-

Chafetz NI, Genant HK, Moon KL, Helms CA, Morris JM. Recognition
of lumbar disc herniation with NMR. AJR 1983;141:1153-6.

Edelman RR, Shoukimas GM, Stark DD, et al. High-resolution surface-

Fraser RD. Chymopapain for the treatment of intervertebral disc
herniation: the final report of a double-blind study. Spine 1984:9:
815-8.

Garvin PJ, Jennings RB, Stern J. Enzymatic digestion of the nucleus
pulposus: a review of experimental studies with chymopapain.

Gentry LR, Turski PA, Strother CM, Javid MJ, Sackett JF. Chymo-
papain chemonucleolysis: CT changes after treatment. AJR 1985:

Gower WE, Pedrini V. Age-related variations in proteinpolysaccharides
from human nucleus pulposus, annulus fibrosus and costal carti-

Gibson MJ, Buckley J, Mawhinney R, Mulholland RC, Worthington
BS. Magnetic resonance imaging and discography in the diagnosis of

Han JS, Benson JE, Yoon YS. Magnetic resonance imaging in the spinal
column and craniovertebral junction. Radiol Clin North Am

Hendry NGC. The hydration of the nucleus pulposus and its relation
40B:132-44.

Hirsch C, Paulson S, Sylvén B, Snellman O. Biophysical and physiolo-
gical investigations on cartilage and other mesenchymal tissues.
VI. Characteristics of human nuclei pulposi during ageing. Acta Or-

Javid MJ, Nordby EJ, Ford LT, et al. Safety and efficacy of chymo-
papain (Chymodacitin) in herniated nucleus pulposus with sciatica. JAMA 1983;249:2489-94.

Konings JG, Williams FJB, Deutman R. The effects of chemonucleo-
lysis demonstrated by computerised tomography. J Bone Joint

Krempef JF, Minning DJ, Smith BS. Experimental studies on the effect
of chymopapain on nerve root compression caused by interverte-

Lipson SJ, Muir H. Proteoglycans in experimental intervertebral disc

McCulloch JA, Macnab I. Sciatica and chymopapain. Baltimore etc:
Williams & Wilkins, 1983.

McCulloch JA, Waddell G. Lateral lumbar discography. Br J Radiol

Modic MT. Surface coil imaging of the spine: correlation with surgical
pathology. Paper presented to the Society of Magnetic Resonance

imaging of intervertebral disc disease: clinical and pulse sequence

Naylor A, Horton WG. Hydrophilic properties of nucleus pulposus of

Plessch J. Der Wassergehalt normaler und degenerierter zwisch-

Smith L. Enzyme dissolution of the nucleus pulposus in humans.


Stern LJ, Smith L. Dissolution by chymopapain in vitro of tissue from
normal or prolapsed intervertebral discs. Clin Orthop 1967:50:
269-77.

Wiltse LL. Chemonucleolysis in the treatment of lumbar disc disease.