Journal of Neurology, Neurosurgery, and Psychiatry, 1976, **39**, 508–513

Chymopapain in the treatment of ruptured lumbar discs[1]

Preliminary experience in 48 patients

J. C. MAROON, R. A. HOLST, AND C. P. OSGOOD

From the Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA

SYNOPSIS The results of chemonucleolysis in 48 patients with lumbar disc disease revealed marked improvement in 58%, slight improvement in 23%, and no improvement in 19%. Serious anaphylactic reactions occurred in two patients. These results and those of other neurosurgical and orthopaedic studies are summarized and compared with the 70% improvement rate obtained with a placebo in a recent double blind controlled cooperative study. Only those few investigators participating in the double blind study are now permitted to use intradiscal chymopapain. It is concluded that the ultimate place of chemonucleolysis, if any, in the treatment of ruptured lumbar discs remains to be determined.

Chemonucleolysis or percutaneous enzymatic intervertebral discolysis was first used clinically in 1963 (Smith, 1964). Twelve years later, despite the fact that over 15 000 patients have since been treated for lumbar disc disease with this technique by over 40 primary investigators, there is still no unanimity concerning its clinical use. Enthusiastic proponents have been counterbalanced by equally zealous critics. In several series, the results have appeared to be at least as good if not better than conventional open surgical intervention (Brown, 1969; Parkinson and Shields, 1973; Onofrio, 1975; Wiltse *et al.*, 1975). In 1974, after reviewing the results of 37 orthopaedic investigators, the Committee on Chymopapain (Discase) of the American Academy of Orthopedic Surgeons (AAOS) (1974) stated that 'the injection of chymopapain is an acceptable (safe within a reasonable degree of medical probability) and effective method of treatment of pain resulting from an abnormal lumbar disc'. The potential widespread clinical effects of this conclusion, however, have been diminished by additional observations on the potential hazards of such treatment (Shealy, 1967; Travenol, 1970; Scoville and Silver, 1975; Sussman, 1975; Watts *et al.*, 1975b).

The nation-wide instructional courses in the basic and clinical aspects of chemonucleolysis sponsored by the AAOS have generated a significant degree of interest in both the neurological and the orthopaedic surgeons who have attended. Despite the pressure for general release of the drug, the caution exhibited by the manufacturer, the Surgical Drugs Advisory Committee of the FDA, and also the American Association of Neurological Surgeons appears justified. A recent preliminary report of the only double blind cooperative study on the clinical effects of chymopapain indicated that a placebo was equally as effective as chymopapain in producing pain relief in patients with ruptured lumbar discs—70% of those treated by each drug (DeSaussure, 1975).

The purpose of this report is to document our preliminary results and complications in 48 patients and to compare them with other recently reported studies.

[1] Supported in part by a grant from the Monsour Foundation, Jeannette, Pennsylvania, USA.

(Accepted 2 December 1975.)

METHODS

SELECTION OF PATIENTS Patients were selected as potential candidates for chemonucleolysis only if they had symptoms of lumbar disc disease with low back and/or radicular pain into one or both extremities and were not relieved after a strict conservative regimen of bed rest, physical therapy, heat, and analgesics. All patients were required to be between the ages of 21 and 65 years and otherwise in good health. Positive physical findings consisted of one or more of the following: (1) positive straight leg raising on the symptomatic side and/or crossed straight leg raising with pain referred to the symptomatic side; (2) mild weakness of the dorsi- or plantar flexors of the foot of an apparently non-progressive and long standing nature; (3) an appropriate sensory loss; and (4) evidence of depressed or absent reflexes consistent with the clinical syndrome. Diagnostic studies in all patients included the routine haematological studies, radiographs of the chest and lumbosacral spine, and electrocardiogram, and a myleogram using iophendylate (Pantopaque) which demonstrated an extradural defect consistent with a herniated lumbar disc. All women underwent pelvic examinations. Electromyograms were obtained when indicated.

Patients were excluded from consideration if they exhibited any one or more of the following criteria: (1) a pending evaluation of or claim for compensation; (2) profound or progressive weakness of muscle groups of the lower extremities; (3) any degree of urinary or anorectal dysfunction; (4) known or suspected pregnancy; (5) previous injection with chymopapain; and (6) evidence of a narrow spinal canal syndrome or other pathology as suggested by physical findings or myelography.

All patients meeting the above criteria were then offered the possibility of participating in the clinical study with chymopapain after being fully informed of the reported complications and experimental nature of the project. A five page instruction sheet in lay language was given to all patients. This explained the history, presumed mechanism, complications, and technical aspects of the procedure. After 24 hours, the patient was again approached to answer any questions regarding the procedure. If he chose enzymatic treatment in place of surgery, a special consent form, approved by our Human Experimental Committee for this purpose, was signed and witnessed.

TREATMENT PROCEDURE On the day of injection, all patients received 1 g cortisone or its equivalent intravenously not less than 90 nor more than 180 minutes before the enzyme injection was to be given. The patient was then given a general anaesthetic in the supine position on a fluoroscopic table in the operating room and then placed into the lateral position and flexed by means of an inflatable pillow beneath the iliac crest. Using image intensification fluoroscopy, a number 18 gauge thin walled 15 cm spinal needle was placed into the midportion of the affected disc from a posterolateral approach beginning 8 cm to 10 cm from the midline. Discography was performed using 0.75 to 1.5 ml meglumine iothalamate (Conray) injected into those discs suspected from physical and radiological examinations to be abnormal. The discograms were then evaluated for correct needle placement as well as for extravasation of contrast agent into the epidural space. No enzyme was injected into any patient in whom there was extravasation of the contrast agent.

Having confirmed the appropriate placement of the needle, 1.0 ml or 2000 units of chymopapain (Discase) was then injected through a sterile filter. The needle was left in place for five minutes to prevent leakage out of the disc space and then withdrawn. During this interval, vital signs including heart rate, ECG, and blood pressure were monitored continuously. Adrenaline and vasopressors were immediately available if needed. If at the end of five minutes the vital signs were stable, the needle was removed and the patient wakened. Postoperative management consisted of analgesics, muscle relaxants, and bed rest for at least 12 hours before bathroom privileges were granted. Walking was encouraged the following day, and additional in-hospital instructions in back care and exercises were given before discharge. Patients who performed sedentary or office work were urged to be away from their jobs for from three to five weeks. Those with more demanding physical requirements were off for variably longer periods of time, depending on the follow-up results.

RESULTS

The duration of symptoms was from one month to 10 years with a median period of 18 months. The period of follow-up ranged from four to 14 months. Those few patients who were not physically examined one or more times after injection were contacted by telephone and asked specific questions regarding their pain, working habits, and post-injection status.

The results are graded according to the following criteria: 'marked improvement' denotes progressive and sustained relief from radicular pain and/or back ache and diminution of clinical signs, similar in pattern to the relief and improve-

ment which follows successful surgical intervention. This category includes other ratings of 'good', 'excellent', and 'symptom-free'. 'Slight improvement' signifies incomplete relief of radicular pain and/or back ache with residuals of one or the other or both, but no incapacitating pain and with some improvement in the physical signs. 'Unimproved' indicates no improvement. This includes categories of 'no relief', 'poor', and 'no change' as well as those patients who had slight improvement but whose signs and symptoms were not sufficiently mitigated to avoid surgical intervention.

Marked improvement occurred in 28 patients (58%). Although single intervertebral discs (L4-5 or L5-S1) were injected in most cases, two patients had two discs injected (L4-5 and L5-S1) and one patient had three discs injected (L3-4, L4-5, and L5-S1) based on the results of physical findings and/or myelography. Eleven patients obtained marked improvement within the period of hospitalization after injection, which was usually three to six days. Ten patients improved between the time of discharge and the first follow-up examination in approximately four to five weeks. Seven patients obtained their maximum improvement between one and three months after injection. All patients returned to their former work.

Slight improvement occurred in 11 patients (23%). Two had injections into both the L4-5 and L5-S1 interspaces, and one patient had an injection into the L3-4 and L4-5 interspaces. The remainder had single injections, into either the L4-5 or L5-S1 interspace. Six of the 11 patients experienced good to excellent relief of pain in the immediate post-injection period, but from three weeks to three months after injection either low back and/or radicular pain returned and only 'slight improvement' could be documented. In five patients there was a slight diminution in pain, usually in the radicular leg component but with a persistence of low back discomfort. The six patients who worked before injection returned to their occupation. Five patients who were off work before injection did not return to their employment after injection.

Nine patients (19%) were rated as 'unimproved'. Seven of the nine had surgical exploration between one and five months after chymopapain injection. The eighth patient was a 25 year old nurse who had a significant aggravation of radicular pain and increased urinary frequency after chemonucleolysis. Surgical exploration seven days after chymopapain injection at the L4-5 and the injected L5-S1 interspace revealed only a slight bulge of the L5-S1 disc. This disc was excised, and the nucleus pulposus had a homogeneously white milky appearance and did not have the particulate characteristics usually encountered in the removal of a lumbar disc. Microscopically, however, our pathologist could not differentiate this disc material from that routinely removed from other surgical cases. This patient improved dramatically after surgical exploration and returned to her nursing activities. Six months later, however, she again developed severe recurrent radicular pain into both lower extremities which required a prolonged hospitalization of three and a half weeks. Repeat myelogram was interpreted as normal, and, with conservative and psychiatric therapy, she improved again to return to her former nursing activities. The ninth patient refused surgery.

In two patients, free fragments of herniated discs were found laterally and in two others, spondylotic ridges were thought to be aetiologically responsible for the radicular pain. In one additional patient, a protruding disc was excised. In all five of these patients, good symptomatic relief of their radicular and/or their low back pain occurred. In three additional patients, surgical exploration was carried out with no significant improvement in the radicular or low back complaints. Two had radicular pain with signs of weakness of the extensor muscles of the foot and a positive straight leg raising sign, but no significant pathology was found at surgical exploration. In a third patient, a bulging L4-5 disc was excised, but again with no significant improvement in the radicular complaints.

COMPLICATIONS An increase in low back pain occurred in most patients and lasted from two to 14 days. This was usually mild to moderate and was controlled with the usual analgesics and muscle relaxants. Severe muscle spasms, however, developed in two patients and required extensive hospitalization for three and a half and four weeks respectively after injection. Morphine gave only temporary relief, ambulation was impossible, and

the pain involved the paravertebral muscles in the lumbosacral area bilaterally, the buttocks, and both legs. Steroids in high doses were administered to both patients with questionable relief. In one, the sedimentation rate was slightly elevated, but tomograms of the lumbosacral area several weeks after treatment showed no evidence of bone erosion. In both patients, complete relief of their previous radicular pain subsequently occurred, and both were eventually classified as being markedly improved.

Four patients developed severe pain into the opposite leg with concurrent diminution of the radicular pain for which the injection was carried out. In one of these four, hyperpathia in the opposite leg lasted approximately six weeks, after which it subsided completely. One patient developed nuchal rigidity, an elevated temperature, and a diffuse macular rash two days after injection. A subsequent lumbar puncture revealed a spinal fluid protein of 0.9 g/l with two lymphocytes/mm^3. Within seven days with symptomatic therapy, the syndrome cleared, and the patient was discharged completely relieved of her radicular pain, which had persisted for six months and was refractory to all conservative therapy.

The most serious complications were anaphylactic reactions that occurred in two patients. In one, immediately after injection, there was a precipitous drop in the systolic blood pressure from 120 to 60 mmHg with a corresponding sinus tachycardia. Immediate intravenous adrenaline was given with a prompt response of the blood pressure and no permanent sequela. In the second patient, approximately six minutes after the injection, as he was being turned from the operating room table to the bed and while still intubated, there was a profound drop in the systolic blood pressure to an unobtainable level and the onset of ventricular tachycardia. Immediate resuscitative measures included intravenous administration of adrenaline, external cardiac massage, and intravenous lidocaine infusion. This patient also made a complete recovery from the anaphylactic reaction, but required subsequent laminectomy because of failure to improve from the chemonucleolysis. A herniated L4-5 disc was removed. One additional allergic reaction occurred secondary to meglumine iothalamate which was injected for discography. The patient developed an immediate macular rash over the upper trunk and extremities and had a drop in systolic blood pressure from 130 to 80 mmHg. This again responded to appropriate intravenous therapy, and no permanent sequelae were noted.

DISCUSSION

In scrutinizing the reported results of chemonucleolysis, one is confronted with the variable criteria used in the selection of patients and in evaluation and also the inherent danger of summating rather small individual series dealing with such a complex problem as 'sciatica'. Enough data are available, however, to at least make comparisons and useful observations.

In the Table we have summarized the results of four neurosurgical groups and also the combined statistics of 37 orthopaedic investigators who presented their results in private patients who had had no prior surgery to the Committee on Chymopapain of the American Association of Orthopedic Surgeons in September, 1973 (Parkinson and Shields, 1973; AAOS, 1974; Onofrio, 1975; Watts *et al.*, 1975a). The failure rate for both groups was an identical 14%. The primary area of difference was in the higher percentage of 'slight' or 'some improvement' and a comparative decrease in the 'marked improvement' in the neurosurgical series. Onofrio's (1975) results stand out as a striking exception, especially in view of his treatment of an additional 170 patients not included in his initial report but in whom the same success rate was obtained.

Although the follow-up has been relatively brief, our findings have been consistent with others in that maximum benefits appear to occur within one to two months after injection. Allowing for a few late failures and possible successes, our results remain virtually identical to those of Watts *et al.* (1975b), with the exception of a significantly higher complication rate.

As has been emphasized by others, this is by no means a 'benign' procedure. A 1% anaphylactic reaction is a frequently quoted figure (Brown, 1969; Travenol, 1970; Watts *et al.*, 1975a; Wiltse *et al.*, 1975), but, in two patients out of our total of 48, life threatening cardiovascular reactions developed, and catastrophe was averted only by immediate and appropriate cardiorespiratory therapy. Both patients received the recommended

TABLE

RESULTS WITH CHYMOPAPAIN IN LUMBAR DISC DISEASE

	Improvement						Total (no.)
	Marked (no.)	(%)	Slight (no.)	(%)	Minimal or none (no.)	(%)	
Neurosurgical results							
University of Pittsburgh	28	58	11	23	9	19	48
Mayo Clinic (Onofrio, 1975)	60	83	5	7	7	10	72
University of Texas—Dallas (Watts *et al.*, 1975b)	59	59	22	22	19	19	100
University of Manitoba*†	29	40	39	54	4	6	72
Total (no.)	176		77		39		292
Percentage		60		26		14	
Committee on Chymopapain of the American Academy of Orthopedic Surgeons							
Total (no.)	4 893		919		914		6 726
Percentage		72		14		14	

*Determined by degree of back pain. †Parkinson (1975)—personal communication.

dose of steroids before chemonucleolysis and neither had a history of allergy to papaya or its derivative products. Also, no technical difficulties with needle insertion or injection were encountered in either patient.

Although mild to moderate low back discomfort is a well recognized sequela of chemonucleolysis, the severity and persistence of the lumbosacral muscle spasm in two patients was truly alarming. Both reported that they had never experienced pain of such intensity, and narcotics in both patients gave only mild relief.

These severe complications as well as the additional problems noted above and also those reported by Watts *et al.* (1975b) stand in contrast to the results of others (Parkinson and Shields, 1973; Onofrio, 1975; Wiltse *et al.*, 1975). In Onofrio's (1975) series of 242 patients, no anaphylactic reactions occurred, and the only complications were limited to three cases of aspiration, presumably secondary to intubation in the lateral position. Parkinson and Shields (1973) have also reported no serious complications. The reasons for this are unexplained and, although unlikely, perhaps are due to chance alone since the technical aspects of the procedure are virtually the same in the hands of all investigators.

Despite intensive investigation into the biochemistry, toxicology, and pharmacology of chymopapain, the precise mechanism by which pain is relieved remains unclear (Watts *et al.*, 1975a). In patients having follow-up myelography, MacNab (1973) reported no significant change in the myelographic defect in a small series of patients. Watts *et al.* (1975b) have suggested that chymopapain may be flushed into a torn annulus and affect the function of pain fibres in this region, thus producing its therapeutic effect. Sussman (1975) suspects that the clinical improvement associated with chymopapain injection derives from such non-specific factors as placebo effect, improper case selection, alkaline wash, or neuronal injury.

In view of the significant number of patients who have been promptly and apparently permanently relieved of pain by chemonucleolysis, the report of the cooperative study using a double blind protocol is particularly intriguing. The observation that 70% of patients given a general anaesthetic and injected with a placebo have obtained relief of pain due to herniated lumbar discs underscores our glaring lack of understanding of the pathophysiology and psychosocial aspects of the pain associated with lumbar disc disease.

White (1968) has warned that when personality factors are unfavourable a poor result is almost certain in the operative treatment of lumbar disc disease, no matter how accurate the anatomical diagnosis or how skilful the surgeon. Recently, Wiltse and Rocchio (1975) evaluated preoperative psychological tests as predictors of success of chemonucleolysis in the treatment of rather rigidly selected patients with the low back syndrome. They found that the hypochondriasis

and hysteria scores of the Minnesota Multiphasic Personality Inventory were reliable predictors of which patients would have excellent and which would have poor symptomatic results. Patients with very low scores (54 and below) were 90% certain of having a good or excellent symptomatic improvement, while only 10% of patients who were extremely high (85 and above), regardless of positive physical findings, showed this degree of improvement. Preoperative ratings by the surgeons of the degree to which the patient's symptoms were psychogenic in origin were also of considerable predictive value.

For the present, the role of chemonucleolysis remains in limbo with clinical application confined only to those investigators participating in the double blind protocol. Its future place, if any, in the clinical treatment of lumbar disc disease must await the further critical, objective, and prolonged evaluation of this multicentre cooperative study.

We are indebted to Mrs. Ellen Narvin for her editorial assistance.

REFERENCES

American Academy of Orthopedic Surgeons (1974). *Report of the Committee on Chymopapain (Discase)*. American Academy of Orthopedic Surgeons: Chicago, Ill.

Brown, J. E. (1969). Clinical studies on chemonucleolysis. *Clinical Orthopedics*, **67**, 94–99.

DeSaussure, R. L. (1975). Special communication to members of the American Association of Neurological Surgeons, Memphis, Tenn.

MacNab, I. (1973). Chemonucleolysis. *Clinical Neurosurgery*, **20**, 183–192.

Onofrio, B. M. (1975). Injection of chymopapain into intervertebral discs: preliminary report on 72 patients with symptoms of disc disease. *Journal of Neurosurgery*, **42**, 384–388.

Parkinson, D., and Shields, C. (1973). Treatment of protruded lumbar intervertebral discs with chymopapain (Discase). *Journal of Neurosurgery*, **39**, 203–208.

Scoville, W. B., and Silver, D. (1975). Results of Scoville and Silver's questionnaire on chymopapain. *Journal of Neurosurgery*, **42**, 487.

Shealy, C. N. (1967). Tissue reactions to chymopapain in cats. *Journal of Neurosurgery*, **26**, 327–330.

Smith, L. (1964). Enzyme dissolution of the nucleus pulposus in humans. *Journal of the American Medical Association*, **187**, 137–140.

Sussman, B. J. (1975). Inadequacies and hazards of chymopapain injections as treatment for intervertebral disc disease. *Journal of Neurosurgery*, **42**, 389–396.

Travenol Research Summary (1970). *Discase*, 2S120, 16.

Watts, C., Hutchinson, G., Stern, J., and Clark, K. (1975a). Comparison of intervertebral disc disease treatment by chymopapain injection and open surgery. *Journal of Neurosurgery*, **42**, 397–440.

Watts, C., Knighton, R., and Roulac, G. (1975b). Chymopapain treatment of invertebral disc disease. *Journal of Neurosurgery*, **42**, 374–383.

White, A. W. M. (1968). The compensation back. *Applied Therapeutics*, **8**, 971–974.

Wiltse, L. L., and Rocchio, P. D. (1975). Pre-operative psychological tests as predictors of success of chemonucleolysis in the treatment of the low back syndrome. *Journal of Bone and Joint Surgery*, **57-A**, 478–483.

Wiltse, L. L., Widell, E. H., and Yuan, H. A. (1975). Chymopapain chemonucleolysis in lumbar disc disease. *Journal of the American Medical Association*, **231**, 474–479.