Late results of treatment of intervertebral disc disease with chymopapain

Dwight Parkinson, M.D.

Department of Neurosurgery, University of Manitoba, Winnipeg, Manitoba, Canada

The authors report a 12-year follow-up review of 33 patients treated with chymopapain (Discase) injection for intervertebral disc disease. This carefully controlled series of patients was treated under local anesthesia in the prone position. Only the single offending disc that correlated with the myelographic and clinical pathology (without the use of discography) was injected with Discase. Anaphylaxis is treated instantly at the first sign of disturbance, and no patients suffered shock. The percentage of patients who were completely cured or improved continues at about 70%. Aside from sensitivity, complications attributable to proper use of the enzyme remain at zero. Follow-up review of those patients over 10 years would indicate that there is no risk of delayed organ toxicity, no risk of carcinogenesis, and no apparent risk of first-generation teratogenesis.

Key Words: chymopapain • follow-up review • carcinogenesis • teratogenesis • organ toxicity • chemonucleolysis • intervertebral disc disease

After a recess of several years, the enzyme chymopapain has reappeared in the United States and is available for general use. At the 1972 meeting of the American Association of Neurological Surgeons in Boston, we presented our results in 33 patients with intervertebral disc disease who were treated by injection of chymopapain; these patients would otherwise have been subjected to surgery. In this small series, with a fairly short follow-up period ranging from 2 to 18 months at that time, our percentage results were essentially the same as those reported by Smith in 1964, and later by Nordby and others. Questionnaires sent out to neurosurgeons by Scoville and Silver revealed that, other than anaphylaxis, there were few if any complications that could be attributed to the proper use of the enzyme. The subsequent history of this enzyme in the United States and its eventual withdrawal from use are described in excellent fashion by Ford. After the product was withdrawn from use in the United States, we in Canada were deluged with requests for the procedure; however, following our original criteria, most of these cases were not submitted to chymopapain injection. We continue to average no more than 30 such procedures per year.

This report describes our follow-up findings in the 33 patients who underwent chymopapain injection.

Clinical Material and Methods

Selection of Patients

We drew up our own protocol that was acceptable to our hospital ethics committee and to the manufacturers of Discase (chymopapain).* The criteria for selection required that the patients:

1. Must be disabled by nerve root involvement so that performance of his/her usual activities (be it playing a violin or working as a stonemason's assistant) is not possible
2. Must have had a reasonable trial of conservative management
3. Must have a myelographic defect that coincides with the clinical picture
4. Must have no other disease that could mimic any part of the clinical picture
5. Must have agreed to surgery as the next step in his/her management.

Less specific exclusions involved patients whose general health or attitudes toward their health were unacceptable. This included patients who were excessively obese.

The first and second criteria are self-explanatory. The third criterion was one of our first major departures from the protocol at the time (in 1969). Myelograms serve the additional purpose of excluding the possibility of a silent tumor higher up. We examine the cerebrospinal fluid fractions. False-negatives decrease directly with the interest, experience, and attention of the myelographer. If swollen roots, cut off roots, and angled takeoffs are carefully noted, laterally displaced discs are

* Chymopapain (Discase) manufactured by Travenol Canada Inc., 6405 Northam Drive, Mississauga, Ontario, Canada.
Discase reappraisal

rarely missed. If more than one intervertebral disc deformity was noted, we injected only the one that we would have cut into if the patient had been treated surgically; that is, only the disc that fit with the clinical picture. We did not inject an adjacent bulging disc simply because it was accessible any more than we would inject or operate on the incidentally bulging lumbar disc found during myelography for higher lesions. We objected to the routine injection of two or more lumbar discs as done by many of the investigators at that time. We recognized that discography like myelography reveals degenerative discs that are not at all symptomatic. We also avoided discography on the basis that if this enzyme were to succeed, it would probably act better undiluted and not mixed with any other material. Anteroposterior and lateral films confirmed correct needle placement in the centrum of the disc.

The fourth criterion excluded patients with diseases that could mimic intervertebral disc disorders. This did not mean that we denied treatment to a patient with diabetes or a demyelinating disease; however, because chymopapain was then being accused of causing neuropathy, we agreed such patients should be excluded from the series.

The fifth item we considered one of the best criteria. We all recognize the difficulty in evaluating the complaint of pain. We are often confronted with patients who say they cannot stand their condition any more, and that something must be done. Yet, when asked if they are ready for an operation, they reply that their pain is not that bad. We asked the patients if they had come to the point where they were ready for surgery, and in the event the injection should fail, were they then ready for surgery? If they said no, then we refused to perform chymopapain injection.

Methods of Chymopapain Injection

We avoided the use of general anesthesia, which was in 1969 being required as a protection against anaphylaxis. We checked with our experts, all of whom agreed that anesthesia would neither prevent nor modify anaphylaxis, but might delay for a few precious seconds that anesthesia would neither prevent nor modify anaphylaxis. We checked with our experts, all of whom agreed in 1969 being required as a protection against anaphylaxis. We avoided the use of general anesthesia, which was in 1969 being required as a protection against anaphylaxis. We checked with our experts, all of whom agreed that anesthesia would neither prevent nor modify anaphylaxis, but might delay for a few precious seconds that anesthesia would neither prevent nor modify anaphylaxis. We checked with our experts, all of whom agreed in 1969 being required as a protection against anaphylaxis.

We used 1 to 2 cc of 1:2000 Discase according to the manufacturer's brochure. We noticed a white reflux in about 8% of the patients, and found that this had no correlation with the results. Most patients experienced a considerable amount of back pain as the 1-cc volume was exceeded. Rarely is the leg pain reproduced. Nothing in our follow-up study indicates that there is any advantage to injecting more than 1 cc of Discase, but nevertheless we try to inject 2 cc if the patient tolerates it. We removed the needle as soon as the injection was completed and turned the patient on his back. The anesthetist with adrenaline-filled syringe followed the patient back to the recovery room. Morphine was prescribed for the back pain and spasm that occurred in about 85% of the patients. The patient was up and about the same day, and with rare exception was dismissed from the hospital the following morning. We did not use a test dose of Discase, and have not given any preoperative cortisone or histamine blockers.

Postoperative Management

The postoperative management begins with the preoperative discussion, during which the patient's expectations and motivations are determined, and his fears allayed. It is emphasized that there is no wound to heal and there is no disturbance of supporting mechanism, and that we know of no disturbance secondary to the procedure that should require more than 4 days to resolve. The standard precautions, such as lifting positions, are emphasized. Patients are told that there is no way to list all the procedures that should be either avoided or indulged. If a particular activity precipitates or aggravates their discomfort, then they are to cut back on that activity. We discuss the fact that some patients experience relief of leg pain within an hour and others experience no relief for some 6 weeks, and then experience a gradual relief that may continue as long as 6 months. They are advised that there may be a consid-
erable amount of back pain and spasm which may last a few hours up to 4 days, but never any longer, and that the patients with the greatest amount of pain often get the greatest amount of relief. (We recognize that patients who experience a gradual relief over weeks or months may well be undergoing the natural course of the disease, and we also recognize that an almost instantaneous relief may be coincidental or due to a placebo effect.) Recognizing that farmers with a crop to get in will be back on their tractors 18 hours a day on the 3rd postoperative day and that patients receiving workers’ compensation may continue to complain of pain for 18 months, we focus on motivation as the greatest single feature. Postoperative management starting with the preoperative discussion is directed mostly at encouraging patients to return to their usual activities within 2 or 3 days, guided by the amount of discomfort they have. Over 60% of our patients with good results were back to their full-time activities within 10 days.

Results

The evaluation of results involves the same intangibles that are involved in patient selection. The patient presents because of subjective complaints, and we have tabulated our results on the same basis, allowing no changes by the examining physician regardless of his impressions. Our percentage results for 200 patients followed from 1 to 12 years are identical to those from our very first report of 33 patients,17 and our subsequent report of 105 patients.18 Approximately 1% reported that they were worse; virtually none reported that they were entirely the same. About 65% reported complete recovery of leg pain, and around 15% reported complete recovery of back pain. Some 75% reported ability to go about all their usual activities, thus indicating that some patients enjoy sufficient improvement of both back and leg pain to return to their full activities even though they have not achieved complete recovery in either.

As the follow-up period is extended, we find that at the 10-year mark 96% of patients are reporting recovery. This has to be the result of the natural course of the disease to a large extent. We have experienced an approximate 5% dropout over the 12-year follow-up period.

Pharmacological Considerations

An enormous amount of work has been done on the pharmacology of this enzyme,2,4,6,8,9,21,23–25 and the exact mechanism of its action is still incompletely understood. It is recognized to be highly specific with no action on collagen, even when used in a concentration many times its therapeutic dosage. It is generally agreed that in some way it modifies the water-binding of the nuclear material. Work in our laboratories has demonstrated an increase in the urinary glycosaminoglycans for 24 hours and no significant increase in the serum concentration of glycosaminoglycans over the same period.2 We have been unable to detect any gross difference in previously injected discs when exposed at surgery: there is no increased vascularity, no unusual amount of adhesion, and no gross change in the disc material removed. We have never encountered an “empty disc space.” We have operated 5 days, 5 weeks, and in three cases several months following injections. The pathologist is unable to recognize any difference in injected discs and ones removed without prior injection. However, most pathologists are not accustomed to search for detailed structural changes in disc material. No doubt, such changes will be found in the future with special investigations, such as scanning electron microscopy, as more attention is given to these features. We have soaked pieces of disc material, dura, and nerve root from autopsy specimens in therapeutic concentrations of chymopapain, changed daily, and have seen no gross differences after 1 week.

Delayed Effects

As with any new drug, concern always exists about the possibility of delayed effects (the thalidomide or “time bomb” effect). When a drug has been used for a long time, such as aspirin, these fears can be safely laid to rest. With other drugs, one can only wait. To date, there are no reports of liver, kidney, lung, or other organ toxicity, nor of autoimmune responses such as occur with other drugs capable of producing sensitivity reactions.19 There is no report of carcinogenicity or any other evidence of chromosome breaks. By this time, any such complications would have come to light with a drug that has been scrutinized by so many individuals from so many viewpoints as has Discase. Some agents, of course, have a latent period of up to 40 years,19 but these are usually on the basis of radioactivity.

Teratogenic aspects have not yet been considered in association with the use of Discase. We recently added a very carefully worded paragraph concerning offspring to our follow-up questionnaire for all patients injected more than 7 years before. Of the 95% who replied, none reported any abnormalities in their children. Thus, so far, first-generation teratogenicity is not a hazard with this particular enzyme.

Summary

We have reviewed our strictly selected, subjectively followed series of 33 patients with intervertebral disc disorders treated with chymopapain injection. The results confirm previously published data regarding improvement and cure percentages, and would indicate that local anesthesia is as safe and possibly safer than general anesthetic during the procedure. When Disease is properly used in the correct dosage, the one specific risk is that of sensitivity. To date, there is no evidence of delayed reaction, organ toxicity, autoimmune disease, carcinogenicity, or first-generation teratogenicity.

References

1. Apfelbach HW, Jacobs RL, Ray RD: Chemonucleolysis

Manuscript received April 18, 1983.
Accepted in final form August 2, 1983.
Address reprint requests to: Dwight Parkinson, M.D., Professor of Neurosurgery, S-111, 750 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0W3.