Treatment of protruded lumbar intervertebral discs with chymopapain (Discase)

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Thirty-three intervertebral disc patients who otherwise would have been subjected to surgery were treated by injection with chymopapain. The pharmacology, toxicology, physiology, immunology, and chemical action of this enzyme, which specifically reacts with chondromucoproteins, are discussed. Results indicate that this method, although still experimental and unapproved by the U.S. Food and Drug Administration, may become a useful addition to the surgeon's armamentarium in the treatment of intervertebral disc disease.

KEY WORDS: protruded lumbar intervertebral disc · Discase · chymopapain · proteolytic enzyme · chondromucoproteins

Chymopapain Action

Pharmacology

The pharmacology, toxicology, physiology, immunological reactions, and chemical action of chymopapain are being continuously studied. Disease is a sterile non-pyrogenic preparation of the proteolytic enzyme chymopapain derived from papaya latex, it is provided in vials containing 10,000 units of the lyophilized agent with 3.4 mg of cysteine hydrochloride and 0.37 mg of sodium edetate. The diluent is USP water for injection. The specificity is such that it takes some 20 times the dosage necessary to react on the chondromucoprotein before there is a visible effect on the adjacent annulus or fibrocartilage of the discs of rabbits and dogs. This specificity of Disease thus makes a protective barrier of the unaffected annulus and fibrocartilage as distinct from...
the situation with collagenase, which is reported to specifically attack fibrocartilage.\(^3\)

In rabbits and dogs, chymopapain dissolves nucleus pulposus at 0.08 to 0.15 mg per disc. Doses up to 100 times this amount were well tolerated intravenously, epidurally, and within the disc.\(^{16,28}\) Sublethal doses up to 10 mg/kg intravenously produce hypertension and hypocoagulability;\(^3\) beyond this dosage, potentially lethal intravenous doses produce systemic and local hemorrhagic reactions related to the rupture of minute blood vessels and to hypocoagulability.\(^4\)

The mode of action on the nucleoprotein is not known for certain but it is postulated that Disease may disrupt the fine structure of chondromucoprotein, thereby destroying its water-binding properties and markedly reducing its capacity to exert pressure.\(^{24}\) This mechanism may explain the rapid relief of sciatica observed in many cases immediately after the injection. Small amounts \emph{in vitro} will dissolve and reduce the viscosity of the water-soluble portions of human nucleus pulposus in a few minutes.\(^{31,34}\)

When one considers that large asymptomatic discs have been demonstrated incidentally during myelography for other conditions, and that there can be a dramatic reproduction of pain following injection of 0.25 cc of fluid into the center of a symptomatic disc, it is not hard to conceive that a small reduction of the central volume of a disc may produce relief of pain by allowing a centripetal relocation of the bulging periphery, even though this relocation is so slight that it is not visible by myelography.

\section*{Reported Complications}

There is an estimated 1 to 1000 possibility of the introduction of infection by the use of a needle. Because the incidence of anaphylaxis is approximately 1 to 100 and there is as yet no satisfactory sensitivity test, Disease is contraindicated in any patient who has been treated previously with this material or who is known to be sensitive to papaya protein. By protocol it may only be used in lumbar discs; its use in pregnant women is forbidden because of the unknown teratological effects.

In another series, up to June, 1972, 86 complications had been reported in a total of 2577 cases injected.\(^7\) These included two deaths:\(^*\) one from coronary artery thrombosis in a 57-year-old woman with long-standing heart disease and severe hypertension, and one from bacterial endocarditis 55 days after injection, with an autopsy finding of a paravertebral abscess at the level of the injection and considerable evidence that the patient may have had bacterial endocarditis prior to the injection. In one case the late development of paraplegia was found at surgery to be associated with adhesive arachnoiditis extending many levels above the site of the Disease injection; this patient had contrast medium retained from a previous myelogram. There have been six cases of discitis diagnosed on the basis of x-ray changes, and all of these have cleared without complication. There have been four cases of pulmonary embolism, two nonfatal cardiac arrests, one cerebrovascular accident, one possible coronary infarct, one case of hypovolemic shock, and 35 patients with varying degrees of sensitivity reaction (1.3\% of the series to that time). There was one instance of transient foot drop, one patient complained of body odor, one of nausea, and one of headache. Other patients had transient ileus and/or urinary retention. With the exception of the foot drop, the discitis, and sensitivity reactions, these complications have been considered nonspecific for this particular procedure in humans when the site, method, and dosage for injection of the Disease have been done as recommended.\(^{28}\) These complications might well be compared with the complications reported following disc surgery.\(^{1,2,18,25,26}\)

\section*{Method}

In 1970 we were asked if we would participate in the investigation of this drug. After studying the protocols and requesting certain changes that were agreed upon by the personnel of the Travenol and Baxter Canada Laboratories, specifically that we would use local rather than general anesthesia\(^\dagger\) and myelograms rather than disco-...
Treatment of protruded lumbar discs with chymopapain (Disease)

grams, we proceeded. This arrangement was also approved by the Ethics Committee of the Winnipeg General Hospital. An anesthetist was always standing by and an intravenous tube connected because of the possibility of anaphylactic reaction.¹⁴

Selection of Patients

Since the start of the study all patients in whom conservative management had failed and in whom surgery had been agreed upon by both patient and surgeon have been offered this alternative. All but two of the patients in this 6-month period elected to try the procedure rather than surgery. The ages in the series ranged from 24 to 79 years, with 21 men and 12 women (Table 1). Each patient had had disabling back and/or leg pain, marked limitation of straight-leg raising, and a myelographic defect at the appropriate level. Only one patient complained of weakness and she had a nearly complete foot drop (Case 24). On examination, however, 29 had demonstrable weakness of the ankle or toes. Fifteen had measurable muscular wasting but none complained of this. Reflex changes and sensory loss did not correlate with the degree of

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* C = calf; T = thigh, B = back; L = leg; SLR = straight-leg raising; Ce = center third of nucleus pulposus; A = anterior third of nucleus pulposus; L = lateral third of nucleus pulposus.
† Patient had previous surgery.
‡ Compensation or Welfare case.

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disability or degree of improvement and hence have been omitted from Table 1.

**Procedure**

We have used the lateral approach, placing a 6 in. No. 18 lumbar puncture needle with the assistance of an image intensifier. A common mistake is to start the needle insertion too far medially. It should be started at least 4 in. lateral to the spinous process in its posterolateral approach to the disc center in order to readily clear the lamina and nerve roots. In aiming at a 5th space, the needle must also clear the posterior portion of the iliac crests and hence should be started through the skin at about the same level as for a 4th disc.

Before injecting we verify the needle position in the center of the nucleus pulposus of the involved disc by obtaining anteroposterior and lateral films as final proof. We inject only those discs that we would otherwise operate upon. To some extent this is a departure from the procedures of the orthopedic investigators who have usually injected two or more discs whereas we rarely inject more than one disc.

Through a 1 cc tuberculin-type syringe we usually inject 1 to 2 cc of a mixture containing 2000 units per cc into each disc space. The needle is left in place for 5 minutes after the injection and then withdrawn.

Even with the needle properly placed there are three variations that the operator may notice during the actual injection (Table 1). The first concerns the ease of injection. In most discs there is a considerable resistance, and if the pressure is released the plunger will recoil 2 or 3 mm. This resistance may increase with the amount injected.

The second variant is the occasional appearance of a white milky reflux as the plunger is released. In some instances shreds of white material enter the syringe or appear at the hub of the needle after the injection is completed and the syringe detached. The third variable is the occasional exacerbation of the pre-existing leg or back pain during the injection even though the procedure is done in such a manner that the patient does not know when the actual injection is being made.

We have been unable to correlate any of these three injection variables with the age of the patient, the placement of the needle, the duration or extent of the disc disease, or the extent of the recovery. We have suspected that the patients showing less than the usual amount of resistance to injection have extensive softening or actual rupture of the containing annulus.

In one patient, a 47-year-old woman not included in the follow-up series, a drop of blood appeared on aspiration after the needle was positioned. The position was re-verified with anteroposterior and lateral films as being in the center of the disc. The needle was withdrawn approximately 1 mm. Aspiration again recovered a drop of blood. The needle was withdrawn, and the procedure discontinued. The patient experienced no untoward reaction. At laminectomy 6 days later, completely extruded disc fragments were removed without incident. Curettage of the disc space revealed no abnormal vascularity. The patient made an uneventful recovery. The pathologist was unable to find any gross or microscopic difference in the submitted material.

**Results**

Most of the patients experienced some back pain and spasm lasting for 1 to 4 days following the injection. Some reported an almost immediate reduction of leg pain while others noted a slower disappearance over the next 2 to 4 days. In a few, gradual improvement continued over 6 months.

After the intradiscal injection of chymopapain in man, a temporary rise in acid mucopolysaccharide excretion in the urine has been reported; this drops back to normal after 1 to 3 days. The mucopolysaccharides excreted were apparently the same as those excreted normally except that they contained more chondroitin 6-sulphate. Since the human nucleus pulposus contains large amounts of chondroitin 6-sulphate, the presumption is that the increased excretion in the urine originates from the intradiscal chondromucoprotein. Early in our series, these excretions were monitored and thought to be quite significant; later they were considered insignificant, and monitoring was discontinued. The blood level is considered a more reliable indicator of the
action but unfortunately could not be continued in our series.  

Three of the 33 patients experienced no immediate relief, and surgery was done within 6 days of the original injections. Each of these had completely extruded disc fragments. There was no gross or microscopic difference between these disc fragments and those from patients not previously treated with Discase.

A questionnaire was sent to the remaining 30 patients asking the status of their leg and back pain, and ability to do their former work. Because neither weakness nor wasting was noticed by any of the other patients, nor considered a disability, it was not put on the questionnaire. Among the patients who also were examined, none showed any residual weakness; even the woman with a nearly complete foot drop and toe drop had regained normal strength.

At the time this paper was presented, 20 patients had responded to the questionnaire, with follow-ups ranging from 2 to 18 months (Fig. 1). Twelve are free of their previous leg and back pain, and four more are free of leg pain and doing all of their usual work. One housewife is free of pain but doing less than the usual amount of work. Another patient, a chronically unemployed recipient of Welfare, is doing the same amount of work as before, namely, nothing. Two patients state that they are worse; both are grievance patients with open compensation claims.

Discussion

In this admittedly small series with a short follow-up, we have not observed any evidence of transient or permanent harm attributable to the procedure and no patients with evidence of an anaphylactic reaction. With adherence to the routine safeguards for accurate needle placement and the manufacturer's recommended dosage and mixture, the procedure has proved safe. As with most clinical trials, there is always more than one variable. We have not tried needle insertion alone, or injection of other active substances or of inert controls. 15, 25. No patient reported being the same as prior to the injection; all are either better or worse. The possibility of suggestion or spontaneous coincidental cure must be admitted, although with the length and severity of the pretreatment history, both seem unlikely. A subsequent follow-up study has extended the original follow-up by an additional 6 months, and there has been no significant change in the incidence or degree of improvement; Fig. 1 still applies. The same two patients who claimed to be worse following the procedure are markedly improved as far as back movements and straight-leg raising are concerned. The latter are the only objective measurements available for either patient, yet they both still claim to be worse, and neither one has settled his prior claims. Miraculous as this drug may appear in its action, it obviously has no effect on the factors that distinguish the grievance patient from the nongrievance patient any more than surgery does.

Since these original cases were reported, we have done 26 additional cases, still with no ill effects and with very similar results. However, the objectivity of this subsequent series has changed in that it can no longer be claimed as an alternative offer to the patient after he has agreed on disc surgery. As the procedure is becoming more widely known in the area, patients are beginning to ask for it instead of disc surgery.

**Fig. 1.** Graph showing the results of the follow-up questionnaire in 20 patients.
References


3. Bownass JM: Personal communication, February, 1972


18. Gurdjian ES, Ostrowski AZ, Hardy WG: Results of operative treatment of protruded and ruptured lumbar discs based on 1176 operative cases with 82 per cent follow-up of 3 to 13 years. J Neurosurg 18:783–791, 1961


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