Experimental Intervertebral Discolysis with Collagenase

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PAIN caused by herniation of the intervertebral disc is relieved by surgical decompression of the affected nerve root. This is accomplished, for the most part, by removal of the protruding nucleus pulposus and fibrocartilage. Usually a limited excision will satisfactorily relieve pain. However, techniques vary among surgeons and once an operation is undertaken, each operator on the basis of his own experience usually extends the procedure to include some individual modification. This may include conservative or radical foramenotomy, major unilateral curettage of the intervertebral joint space, or bilateral total discectomy. The dialogue continues between neurosurgeon and orthopedic surgeon regarding the indications for spine fusion. Most surgeons, however, are aware of the favorable results that often follow conservative removal of the herniated portion of the intervertebral disc. This consideration has led to speculation concerning the feasibility of achieving this same degree of nerve root decompression non-surgically by selective enzymatic dissolution of the underlying and protruding disc. If successful, such a technique would extend the possibility of treating patients by conservative methods. This paper deals with experimental studies conducted in the dog, using the enzyme Collagenase* for intervertebral discolysis.

The properties of the enzyme have been reviewed by Mandl, et al.1 These biological characteristics, along with preliminary evidence of the effect of collagenase upon nucleus pulposus and fibrocartilage removed from the human, have been reported.4 Collagenase appears to be a unique microbial enzyme with regard to its capacity to attack native collagen under physiological conditions of pH and temperature. This is significant because unaltered collagen is ordinarily resistant to all common proteolytic enzymes. Furthermore, its enzymatic action is attended by high specificity for collagen and inability to attack protein substrates, such as casein or hemoglobin, the fibrous proteins, fibrin, keratin, and elastin, or epithelium. This specificity assures a margin of safety not shared by the common proteolytic enzymes. Use of the latter for these same purposes has been attempted,5 but complications have occurred. In particular, proteolytic enzymes such as chymopapain have produced widespread tissue necrosis and hemorrhage and this has resulted in justifiable scientific reservations regarding their use.2

Material and Method

For this study, 16 mongrel dogs were used. They were divided into three groups, the first receiving a smaller dosage of collagenase injected locally, the second receiving a larger dosage injected intrathecally, and the third group being used as controls.

Group 1. Operative exposure of the lumbar intervertebral disc space was carried out in 10 adult mongrel dogs under intravenous sodium pentobarbital anesthesia. Two animals were relatively young as evidenced by subsequent microscopic demonstration of vertebral epiphyseal plates. In nine animals, the surgical approach was made through the lower abdominal cavity by transperitoneal exposure, and in one animal, translumbar retroperitoneal exploration was performed. Preliminary x-ray studies of the lumbar spine were carried out. With a 20-gauge needle, 1 cc of sterile solution containing 1 mg of collagenase was injected through the anterior longitudinal ligament into the nucleus pulposus. Resistance to insertion of the needle and evaluation of lateral x-rays of the spine determined satisfactory placement of the enzyme. The needle was then advanced farther posteriorly until it penetrated the posterior longitudinal ligament; an additional

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1 mg of collagenase was then injected into the spinal canal. Radiopaque identification of the adjacent vertebral body was carried out, and the wound was closed routinely.

Complete blood count and urinalysis were determined preoperatively and every third day postoperatively. Clinical observation of the animals, including temperature and pulse rate as well as neurological examination, was continued until their sacrifice 2 to 11 days following surgery. At that time, post-operative x-rays of the lumbar spine were carried out. Removal of the lumbar spine was then performed including the intervertebral spaces rostral and caudal to the injected space. Longitudinal hemisection of the specimen was followed by photographic and histological study.

Group 2. Lumbar laminectomy was performed in four adult mongrel dogs under intravenous sodium pentobarbital anesthesia. In two animals, 2 mg of sterile collagenase in 0.1% solution were injected into the intradural space. In a third animal, the same quantity of enzyme was placed in the extradural space. The fourth animal received a total of 4 mg of collagenase divided equally between the extradural and intrathecal spaces. Routine closure was carried out in multiple muscle and fascial layers using silk technique.

After 7 days, the first three animals were sacrificed. Further laminectomy was performed, and the dural sac containing the lumbar spinal cord and nerve roots was removed for histological study. The animal that received extradural placement of the enzyme received additional study of the adjacent skeletal musculature. The fourth animal was saved for long-term survival.

Group 3. Transperitoneal operative exposure of the lumbar intervertebral disc space was carried out in two mongrel dogs. Preliminary x-ray studies of the lumbar spine were obtained. Then, with a 20-gauge needle, 1 cc of normal saline was injected through the anterior longitudinal ligament into the nucleus pulposus. Radiographic confirmation of accurate needle placement was obtained, and radiopaque identification of the disc space was made.

Postoperative observations were carried out as in Group 1. The animals were sacrificed 8 days after surgery at which time roentgenographic and pathological studies were performed following longitudinal hemisection of the vertebral column.

Results

All dogs walked immediately after recovering from anesthesia and showed no evidence of motor, sensory, or sphincter dysfunction. There was no elevation of temperature, alteration of pulse rate, or change in urinalysis. The blood count was unaltered except for a mild leukocytosis in four animals. Appetite was unaffected. Autopsy failed to reveal any evidence of hemorrhage into the wound or abdominal cavity.

Group 1. In all dogs except Dog 4, a major enzymatic curettage of the disc space was accomplished (Figs. 1 and 2). In Dog 4, in spite of open exposure, histological study revealed eccentric placement of the needle with failure of the injected material to enter the disc space. In the nine dogs satisfactorily injected, gross and microscopic examination revealed essentially total destruction by lysis of the nucleus pulposus and major dissolution of the fibrocartilage (Fig. 3). The untreated intervertebral spaces adjacent to the injected space served as the control study in each animal. Details of the microscopic study are shown in Table 1. It may be noted that hyaline cartilage remained intact except for solitary areas of focal necrosis in three cases, which may have been related to needle penetration (Fig. 4), and for one instance of diffuse damage. In two of these animals, some injury of the adjacent bony plate was encountered with marrow fibrosis and cartilagenous metaplasia.

Group 2. In the two dogs that received intradural injections of collagenase, the spinal cord and adjacent nerve roots were morphologically intact (Fig. 5). Sections of spinal cord were stained by hematoxylin and eosin, Weil-Weigert, and thionin (Nissl) methods. There was no evidence of inflammation in either the gray or white matter of the spinal cord. Demyelination of long tracts was not present. One animal showed hyperemia involving the anterior spinal artery as well as changes consistent with acute swelling affecting some of the anterior horn cells. The second showed mild hyperplasia of the arachnoid. Special stains, however, failed to demonstrate chromatolysis or loss of Nissl sub-