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Two Anaphylactic Deaths After Chemonucleolysis

Prior to the early 1960s, treatment of low back pain ascribed to discogenic disease was a choice between a conservative, nonsurgical regime of rest, physiotherapy, and supportive measures, or laminectomy. In 1963, Smith began to inject the drug chymopapain into lumbar disks in patients with low back pain and sciatica [*1*]. This procedure is now called chemonucleolysis. The purpose of such injections is to depolymerize the cementing protein of the chondromucoprotein complex, reducing the molecular size and viscosity of the nucleus pulposus, thus chemically decompressing the disk space [*2*]. Anaphylaxis after the injection of chymopapain has been reported [*3–6*]. The two cases herein reported, however, are the only known deaths due to anaphylaxis.

Case Reports

Case 1

A 45-year-old white female was admitted with the acute symptoms of a herniated disk and sciatica. Chemonucleolysis was performed under general anesthesia (halothane). Preanesthetic medication consisted of 100 mg intramuscular (IM) Solu-Cortef®, Benadryl® (25 mg IM), Demerol® (50 mg IM), and atropine (0.4 mg IM). Fluids were started preoperatively with an intravenous catheter.

Needles were inserted into disk L-4 with the standard lateral approach. They were checked by X-ray and found to be satisfactorily positioned. Renografin® was then injected. A discogram revealed degeneration of the disk and postepidural flow. After waiting ten minutes, 1 cm^3 of chymopapain was injected into the space. Four minutes later as the needles were withdrawn, the blood pressure became unobtainable and the patient was noted to have cutis anserina ("goose flesh"). An oropharyngeal airway was in place at this time. Resuscitative measures were begun. One hundred milligrams of Solu-Cortef® and 25 mg of Benadryl® were administered intravenously. The patient seemed to respond. However, as she was returned to the recovery room, she became worse and died approximately 1 hour and 35 minutes after the beginning of the anaphylactic reaction.

At autopsy, exploration of the needle track from the right lateral back to the intervertebral disk space demonstrated no significant hemorrhage, no laceration of any major blood vessels, and no entrance into the abdominal cavity. Grossly, the intervertebral disk at L-4 was unremarkable. Microscopic sections of intervertebral disks L-4 and L-5 revealed some fragmentation of the material of both disks. The rest of the autopsy was unremarkable.

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Case 2

The second patient was a 29-year-old white female, admitted to the hospital with a complaint of low back pain with radiation into the left hip and leg to the calf. She had cramps and numbness in the left foot. The clinical diagnosis was herniation of the nucleus pulposus. A myelogram showed no conclusive evidence of a herniated disk. The posterior aspect of L-5 did show, however, a ventral defect, possibly representing a bulging midline, flat type of herniation. An electromyograph was consistent with bilateral L-5 root irritation.

Chemonucleolysis was conducted under general anesthesia (Penthrane®), using the lateral approach. An endotracheal airway was in place. The pre-anesthesia medication consisted of Solu-Cortef® (50 mg IM), Benadryl® (25 mg IM), Demerol® (75 mg IM), and atropine (0.6 ng IM). Needles were inserted into disks L-4 and L-5 and Renografin-76® was injected. Disk L-4 appeared normal, while L-5 showed degeneration. Fifteen minutes after the injection of Renografin-76®, 1 cm^3 of chymopapain was injected into disk L-5. Immediately after the injection, the patient was noted to have dry, warm, flushed skin with cutis anserina. Blood pressure was unobtainable. The pulse rate went from 85 to 160/minute, stabilizing at 120/minute. Cardiac monitors at this time showed no evidence of cardiac anoxia. The patient was treated with Regitine®, Solu-Medrol®, and sodium bicarbonate. This was followed by atropine and Intropin®. The patient was then transferred to the recovery room. Blood pressure was still unobtainable. A cutdown of the left brachial artery produced no bleeding. A catheter, inserted as far as the subclavian artery, revealed no blood pressure. Urine output was virtually nil.

Examination two hours after the reaction revealed no peripheral pulses and no obtainable blood pressure. Palpable pulses were present bilaterally in the carotid and femoral areas. The usual bounding aortic pulse was not present. There was no urinary output at this time despite administration of Lasix®, Mannitol®, and intravenous fluids.

Approximately 12 hours after the reaction, the patient began to respond neurologically. She began talking and moving her extremities without any pain. Blood pressure was still extremely low, 40/40 and 60/40 mm mercury (Hg). Urine output was nil. The abdomen was distended at this time, and no bowel sounds were heard.

Approximately 24 hours after the reaction, the blood pressure was poorly obtainable with a level of 60/20 mm Hg. The abdomen appeared distended, and an abdominal X-ray showed air in the abdominal cavity. The patient's temperature was 102.6°F (39.2°C).

Twenty-six hours after the anaphylactic reaction, the patient was brought to the operating room a second time for an exploratory laparotomy. When the abdomen was opened, the small bowel and the ascending colon were noted to be infarcted. The patient died on the operating table.

An autopsy was performed the morning after the death. Examination of the needle track from the right lateral back to the vertebral column showed that the needle never entered the abdominal cavity. There was no significant hemorrhage and no major blood vessels were injured. Examination of the spinal column and vertebral disks in the lumbosacral region revealed no significant differences in the appearances of the disks both grossly and microscopically in spaces L-4 and L-5. There was posterior herniation of the disk of L-5. The small bowel, distal to the ligament of Treitz and the large bowel, up to the area of the hepatic flexure, was infarcted with transmural necrosis of the wall. Microscopic infarcts were present in both adrenal glands. Infarcts were also present in the spleen. A 3 by 3 cm area of hemorrhagic infarction was present in the left lobe of the liver. No thromboses were present in either the arterial or venous systems.

Comment

Chemonucleolysis as a method of therapy for discogenic disease has the advantages of

simplicity of technique, good results, and the fact that failures can still be subjected to operative therapy. At the present time, chymopapain is still an experimental drug in the United States. It is, however, in the last stages of investigation and approval for more general use is expected shortly.

More than 15 000 cases have been treated by chemonucleolysis world-wide. Anaphylaxis following the injection of chymopapain has occurred in about 1% of these cases [*3*]. Because of this danger, reinjection of chymopapain after an initial injection of this drug is forbidden by the experimental protocol under which chymopapain is being tested. This stipulation is to prevent an initial injection from sensitizing an individual to chymopapain. Indeed, one of the nonfatal cases of anaphylaxis in the literature is in an individual who had received a previous injection of chymopapain [*4*]. In another individual who had an anaphylactic reaction, a subsequent investigation revealed that the patient knew she was allergic to a meat tenderizer, while a third patient developed antibodies to chymopapain after an anaphylactic reaction [*5,6*].

At the present time there is no way to determine which patient will develop an anaphylactic reaction after the injection of chymopapain. Efforts are being made by the supplier of this drug to develop a test to identify such individuals.

The two cases presented are the only known deaths due to anaphylaxis from chymopapain. Both patients developed cutis anserina and abruptly became hypotensive shortly after injection of the drug into the disk. Neither patients showed any significant response to vasopressor drugs. The first patient never came out of shock, dying approximately 1 hour and 35 minutes after onset of the anaphylactic reaction. This patient was receiving halothane. This anesthetic agent is not recommended for chemonucleolysis because epinephrine with halothane is contraindicated as the anesthetic sensitizes the heart to epinephrine [*3*].

The second patient died as a result of complications of the prolonged episode of hypotension. The infarcted bowel in the distribution of the superior mesenteric artery as well as the infarcts of the adrenal gland, spleen, and liver were apparently due to sluggish perfusion of the abdominal organs.

In conclusion, it should be pointed out that the two anaphylactic deaths after chemonucleolysis do not detract from the proven usefulness of this therapy in the treatment of discogenic disease. Any procedure or medication no matter how benign has some morbidity and mortality attached to it.

Summary

Chemonucleolysis is a procedure for treatment of low back pain due to discogenic disease in which the drug chymopapain is injected into lumbar disks to produce chemical dissolution of the nucleus pulposus. More than 15 000 cases have been treated by chemonucleolysis world-wide. Anaphylaxis after the injection of chymopapain occurs in about 1% of such cases. The two cases described in this paper are the only known deaths due to anaphylaxis. Both patients suddenly became hypotensive after injection of chymopapain into a disk. One patient died shortly after this, whereas the second patient died of the complications of prolonged shock.

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