Sensitivity Reactions to Intradiscal Injection of Chymopapain during General Anesthesia

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Chymopapain‡ is a proteolytic enzyme that has been evaluated for treatment of lumbar intervertebral disc disease. It is obtained from crude papain, derived from the plant *Carica papaya*.[1] It is injected intradiscally, usually with the patient under general anesthesia. The procedure, called "chemonucleolysis," was introduced by Lyman Smith in 1964.[2] Approximately 14,000 patients have been treated by chymopapain chemonucleolysis, and various complications have been reported.[3] Most of these, such as discitis, both aseptic and septic, arachnoiditis, and additional neurologic deficits, are delayed in onset. However, many severe sensitivity reactions of immediate onset have been reported. At least two deaths are known to have occurred in this manner.[4]

CLINICAL DATA

The following report deals with four patients who had sensitivity reactions of varying severity immediately following injection of chymopapain. Each patient was premedicated with 50 mg meperidine and 25 mg hydroxyzine, im. After suitable oxygenation, each patient was given approximately 200 mg sodium thiopental and 40 mg succinylcholine, the trachea was intubated, and the patient was placed in the left lateral decubitus position. General anesthesia was maintained with 0.5–1 per cent halothane in O_2. The back was prepped and draped surgically. Under fluoroscopic control, needles were placed percutaneously into the third, fourth, and fifth lumbar disc spaces via a right lateral approach. The needle positions were confirmed by anteroposterior and lateral roentgenograms: then 1.0 ml of a radiographic water-soluble contrast agent (Renografin-76) was injected into each disc space. This not only confirmed the location of the tip of the needle, but permitted evaluation of the disc for degeneration and/or rupture. Approximately 4 mg chymopapain were then injected into each space.

REPORT OF FOUR CASES

Case 1. Within moments of the injection of 4 mg chymopapain into a 66-year-old man, 30 minutes after induction of anesthesia, the blood pressure was 70/50 mm Hg. During hospitalization prior to chemonucleolysis, the patient's diastolic blood pressure had remained above 80 mm Hg. The hypotension responded immediately to administration of ephedrine (25 mg, iv). Additional ephedrine was needed intermittently over the next two hours in the recovery room for maintenance of normal blood pressure. Recovery was uneventful. The patient had received 100 mg hydrocortisone and 50 mg diphenhydramine, im, preoperatively, and was receiving hydrocortisone, iv, at the time of the chymopapain injection. No other evidence of sensitivity was manifested by this patient.

Case 2. A 60-year-old woman had a petechiae-like cutaneous eruption within minutes of injection of 4 mg chymopapain. The eruption spread over most of the trunk, fading as it reached the extremities. The patient was given hydrocortisone, iv, immediately, and intermittently over the next three hours. By inadvertence, she had not received steroid medication preoperatively or during the procedure prior to the development of the rash. No permanent sequelae were seen.

Case 3. A 25-year-old woman became hypotensive and had an urticarial eruption over her entire body, including the palmar surfaces of her hands and plantar surfaces of her feet, minutes after injection of 4 mg chymopapain into each of the fourth and fifth lumbar discs. She had intermittent hypotension and pulmonary wheezes, and was given hydrocortisone and epinephrine, iv, immediately, and periodically over the next few hours. Inadvertently, she had not received steroids preoperatively or intraoperatively prior to the onset of the reaction. After four hours of

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treatment her condition stabilized, and recovery was uneventful.

Case 4. Two minutes after injection of 4 mg chymopapain into the L5, S1 disc space, a 32-year-old white woman was found to have tachycardia (160/min) and a blood pressure of 80/40 mm Hg. Ephedrine, 25 mg, iv, was given immediately. Within 3 minutes blood pressure was unattainable. At this point no femoral or brachial arterial pulsation could be palpated. The distal portions of all four extremities were pale, with prolongation of the digital compression responses. Faint carotid pulsations were detectable. Epinephrine, 0.3 ml (1:1000), was given iv. Within 3 minutes, palpation of a femoral pulse was possible and carotid pulsations improved. No brachial blood pressure could be recorded. Intravenous fluids were given very rapidly. Over the next two hours the patient received approximately 4 liters of balanced salt solutions. Anesthesia was Innovar, 2 ml, plus a 50 per cent oxygen–nitrous oxide inhalation mixture. Immediately upon onset of hypotension the patient was given 100 per cent oxygen. Despite this, the postanesthetic arousal period was prolonged (45 minutes). Despite the rapid infusion of balanced salt solution, it was approximately an hour before significant urinary output occurred. After 30 minutes of hypotension, during which auscultation of blood pressure was impossible, a blood pressure of 70/50 mm Hg was recorded by brachial oscillometry. Two hours after the injection of chymopapain, a blood pressure of 100/70 mm Hg was detected in the left brachial artery. The patient, although comfortable, continued to have tachycardia of 110–120/min for several hours. Approximately 12 hours after the injection of chymopapain, she was asymptomatic. Urinary output was adequate. The patient had received 100 mg hydrocortisone and 50 mg diphenhydramine, im, preoperatively, and had received hydrocortisone, iv, at the time of chymopapain injection. No neurologic, cardiovascular, or renal sequel was noted at the time of discharge or upon further examination three weeks later.

Discussion

Chymopapain is a proteolytic enzyme that catabolizes intradiscal protein–mucopolysaccharide complexes and hastens the formation of intradiscal collagen.[5] Several days after injection of chymopapain intradiscally, urinary mucopolysaccharide excretion increases. Since some patients who have received chymopapain under local anesthesia have reported immediate cessation of symptoms, particularly sciatica,[6] it is felt that chymopapain may alter the function of pain fibers located in the posterior longitudinal ligament and the disc annulus.[7]

The etiology of the sensitivity-type reaction that occurs during chemonucleolysis is unknown. As a proteolytic enzyme, chymopapain is potentially antigenic. One patient known to be allergic to Adolph's Meat Tenderizer (which contains a derivative of the papaya plant) developed an anaphalactic reaction during chemonucleolysis.[8] Sensitivity to chymopapain has been shown to develop following multiple injections in guinea pigs and rabbits.[9] However, repeated injections in man have produced no allergic symptom.[10]

Some investigators have postulated that chronic disc disease with associated pain might in some cases be an autoimmune phenomenon.[11] Although this has not been proven experimentally, it has been shown that the protein–mucopolysaccharide component of human disc tissue can serve as an antigen in the rabbit.[12] Also, patients receiving intradiscal hydrocortisone for primary intervertebral disc disease have had remissions of their symptoms.[13] It is conceivable that in some patients autoantibodies, possibly of an IgE type, are formed during the chronic, preoperative disease state of the disc. The rapid hydrolysis of intradiscal protein–mucopolysaccharide complexes might release into the blood stream substances capable of triggering an acute anaphylactic reaction.

Although it is possible that the contrast agents used during discography might at least contribute to the sensitivity reactions, no investigator has considered this explanation.[6,10,16] None of the patients reported here had previously received contrast agents intravenously.

Sensitivity reactions occur in approximately 1 per cent of these instances.[7] Therefore, patients undergoing chemonucleolysis should be carefully monitored, with airway control and availability of agents useful in the treatment of anaphylaxis. Preoperative administration of steroids is considered indicated.

Although most of our patients were anesthetized with a halothane–oxygen technique, halothane may not be the anesthetic of choice because of the possibility of cardiac arrhythmias should epinephrine be needed in the treatment of an anaphylactic reaction. A technique utilizing a nitrous oxide–oxygen narcoleptic combination has been recommended.[14]

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Authors' note: As of July 1975, all clinical investigation of chymopapain has ceased, except double-blind studies comparing the drug with a placebo. Because the initial data, unpublished, reveal no difference between chymopapain and placebo in effectiveness, it is anticipated that a new drug application will not be granted by the Food and Drug Administration in the near future.

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Potentiation of Succinylcholine Neuromuscular Blockade by Lithium Carbonate

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Lithium was first used by Cade[1] in the treatment of manic-depressive psychosis in 1949. Recently, its use has increased and broadened to include other psychiatric disorders.[2–4]

One previous report described a case of prolonged neuromuscular blockade with pancuronium bromide in a patient on chronic oral lithium therapy.[5] The present report describes a case of prolonged neuromuscular blockade following succinylcholine in a patient being treated by chronic oral administration of lithium. This clinical observation has been substantiated in the laboratory.

Report of a Case

A 38-year-old Caucasian woman with a history of manic-depressive psychosis was seen at 38 weeks' gestation in active labor. Serum lithium levels were reported to be 1.2 mEq/l while the patient was taking 1.5 g lithium carbonate daily, orally. Physical examination disclosed no abnormality except massive obesity (weight 320 pounds). An emergency cesarean section was performed because of fetal bradycardia. Anesthesia was induced with pancuronium bromide, 0.5 mg, thiopental, 350 mg, and succinylcholine, 150 mg, iv, followed by a succinylcholine drip (approximately 310 mg succinylcholine, total, in 120 minutes). A 5 pound, 6 ounce, female infant (Apgar scores 5 and 9) was delivered uneventfully.

Postoperatively, the patient remained apneic for

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