The Food and Drug Administration (FDA) recently has re-released chymopapain, an injectable proteolytic enzyme used as an alternative to lumbar laminectomy in selected patients. The reported success rate, over 80%, has inspired an increasing usage of chymopapain. However, there is a reported 1% incidence of anaphylaxis upon injection of this drug. The authors describe the means of early recognition of signs and symptoms of anaphylaxis. A suggested anesthetic plan is presented that includes a protocol for management of anaphylaxis.

Chymopapain is an enzyme from the tropical tree *carica papaya*. It was first isolated in 1941 by Jansen and Balls.¹ L. Smith, an orthopedic surgeon, began experiments with chymopapain in 1959. One year later he injected the first patient with chymopapain and described this treatment modality, injection into a herniated disc, as chemonucleolysis.²,³ Basically, this technique involves the injection of chymopapain into the nucleus pulposus with a subsequent digestion of that part of the disc relieving compression of the adjacent nerve root.⁵

In 1975, the FDA published an evaluation of chymopapain which emphasized that it would soon be approved for use.⁴ However, this evaluation was scrutinized by various investigators who charged that chymopapain had never been subjected to an unbiased double-blind study.⁵,⁶ This controversy continued as chymopapain injection became available for use in centers where double-blind studies would be conducted.

The use of chymopapain appeared to be ended when the completed double-blind studies indicated no significant difference between chymopapain and placebo injections. The manufacturer of chymopapain withdrew its application for approval from the FDA.⁸ However, in Canada, chymopapain continued to be utilized with reported good results.⁹,¹⁰

Because personnel at the manufacturer of chymopapain (Smith Laboratories) were of the opinion that chymopapain had not been given fair evaluation, they conducted a double-blind study to evaluate its effectiveness. Chymopapain injections were found to be effective in 44 of 55 patients upon evaluation six weeks after the injection. As a result, in November, 1982, following 23 years of controversy, chymopapain (Chymodiacitin) was approved by the United States FDA for clinical use based on a reported 80% success rate.¹¹

N. Hendry has proposed that in a normal nucleus pulposus, the stresses are evenly distributed.¹² When a herniation occurs, the normally high water-binding capacity of the disc is impaired with consequent uneven distribution of the intradiscal pressure.¹³

The precise mechanism of action of chymopapain disc injection is not known. In vitro portions
of the water-insoluble components of nucleus pulposus, from normal or prolapsed discs, are dissolved rapidly by chymopapain.\textsuperscript{13,14} Some investigators believe the rapid hydrolysis of intradiscal protein-mucopolysaccharide complexes following chymopapain injection might release substances into the bloodstream capable of triggering an acute anaphylactic reaction.\textsuperscript{15} These substances and/or chymopapain alone may be the cause of anaphylactic reactions in susceptible individuals.

Chymopapain has a highly selective action. Within the prescribed protocol there is a wide margin between therapeutic and toxic doses. It has been demonstrated in animal models that chymopapain has a several hundred-fold margin of safety when properly injected into the intervertebral disc.\textsuperscript{16} The dura acts as a barrier to the spread of chymopapain, rendering its action on the insoluble portion of the nucleus pulposus minor or non-existent.\textsuperscript{16} Each milliliter of chymopapain contains 2,000 units of the enzyme. The recommended dosage is 1 to 2 ml per herniated disc.

The difficulty encountered with this treatment modality is the relatively high incidence (1\%) of anaphylactic reaction to the intradiscal injection of chymopapain.

**Mechanism of anaphylaxis**

The term anaphylaxis was first coined in 1902 by Portier and Ricket to describe the profound shock and subsequent death that occurred in some dogs when rechallenged by the injection of sea anemone toxin.\textsuperscript{17}

Anaphylaxis is an acute, severe systemic reaction caused by histamine or other mediators being released from basophils and mast cells as the result of an antigen-antibody reaction.\textsuperscript{18} When a specific allergen is injected directly into the circulation it can react in widespread areas of the body with the basophils of the blood and the mast cells located immediately outside the small blood vessels.\textsuperscript{10} Thus, the anaphylactic reaction may disseminate rapidly throughout the body.

In anaphylaxis, a hypersensitive state develops. (See Herriotts in this issue for a complete case study.) Hypersensitivity denotes the capacity of an individual to hyperreact to an agent to which the individual has been previously exposed. Another type of hypersensitive response is the anaphylactoid reaction. The clinical manifestations of an anaphylactoid reaction are indistinguishable from those of an anaphylactic reaction, although the pathophysiology is different.

In an anaphylactoid reaction, the release of histamine is not dependent upon production of antibodies as a result of previous exposure to an antigenic substance. An anaphylactoid reaction is not immunologically mediated, but rather a direct response to mediators released from mast cells or basophils. The injection of an implicated drug induces degranulation of the cell, resulting in hypotension and urticaria. Morphine and d-Tubocurarine are examples of two drugs that can induce a generally minor anaphylactoid reaction when rapidly administered.

In contrast, an anaphylactic reaction is an immunologically mediated, immediate, and massive systemic reaction. Anaphylaxis requires previous exposure to a drug or chemically similar substance and the production of antibodies to this drug. The action of pharmacological mediators at the receptor site causes subsequent clinical manifestations. Severe systemic reactions to chymopapain intradiscal injections are classified as anaphylactic. However, it is not necessary to categorize severe allergic reactions as anaphylactoid or anaphylactic, as the treatment approach is the same.

The predominant clinical signs of anaphylaxis occur as cardiovascular, respiratory and cutaneous manifestations. Any one or all of the manifestations can occur following chymopapain injection.

Cardiovascular signs may consist of moderate to severe hypotension, tachycardia, supraventricular or ventricular dysrhythmias, and/or absence of pulse. In the awake patient, profound hypotension is initially displayed as sudden light-headedness or loss of consciousness.

Respiratory signs may consist of coughing and wheezing due to bronchospasm, and/or hoarseness, stridor and dysphagia due to laryngeal edema. In the event of severe bronchospasm and/or laryngeal edema, there may be no audible breath sounds. Rales and frank pulmonary edema may also occur in an anaphylactic reaction due to rapid fluid shifts and increased tissue permeability.

Cutaneous manifestations may include piloerection, localized or generalized urticaria, and angioedema. Often the eyelids become markedly edematous.

Clinical signs in an allergic reaction, in order of frequency, are: skin changes; hypotension with tachycardia; and bronchospasm resulting in arterial hypoxemia.\textsuperscript{20}

The etiology of anaphylaxis occurring during chemonucleolysis with chymopapain is unknown. However, it is known that chymopapain is a proteolytic enzyme and the nucleus pulposus consists of a protein. Therefore, the injection of chymopapain and the subsequent hydrolysis of the disc protein may release mediators into the bloodstream.
that are capable of producing an anaphylactic reaction.

Immunoglobulins (antibodies) are formed by the body in lymphoid tissue and plasma cells as a response to being exposed to an antigen. Immunoglobulin E (IgE) is a major type of antibody genetically mediated and synthesized by the body.21 In a normal population, one in 5,000 immunoglobulin molecules are of the IgE type, whereas allergic individuals seem to produce larger proportions of IgE that become manifest during the acute hypersensitivity of anaphylaxis.21 The IgE has an affinity for binding to mast cells, basophils, or platelet cell membranes. The receptor sites for bound IgE are primarily in the respiratory and gastro-intestinal tracts and the intravascular space. The events that follow exposure to an antigen (allergen) are collectively termed sensitization. Once an individual is thus sensitized, the potential for a hypersensitive response is present (Figure 1).

Antibodies are complex protein molecules produced by plasma cells and some lymphocytes. Antibodies possess the quality of "specificity" in order for the antigen to fit together with the antibody like a lock and key.21 Upon a subsequent exposure, "locking" occurs. The antigen locks with the specific IgE antibodies attached to the mast cell and triggers a response, releasing mediators. Upon activation, Ca++ and Mg++ migrate into the mast cell and mediators are released (Figure 2).

The primary pharmacological mediators presently known to be associated with immediate hypersensitivity are histamine (H), slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), prostaglandins, kinins, and the platelet aggregating factor (PAF). (Figure 3).

Histamine, the primary vasoactive mediator, causes local vascular dilatation, contracts visceral smooth muscle, increases capillary and venule permeability and causes vasodilatation.19,21 The cardiovascular manifestations are largely attributable to the permeability of vessels with loss of plasma from the intravascular space. Diminished circulating blood volume causes hypotension, with capillary vasodilatation seen as a contributing factor. Vascular dilatation with resultant increased capillary pressure also causes increased capillary permeability. The formation of edema is promoted by "gaps" between endothelial cells. Clinically significant forms of this resultant edema are angioedema and laryngeal edema.

The vasoactive mediators, histamine and SRS-A, contract smooth muscle and stimulate exocrine gland secretion. Effects on the lungs during systemic anaphylaxis would consist of bronchospasm, pulmonary edema, and copious secretions. As an isolated substance, SRS-A causes prolonged contraction of smooth muscle with resultant bronchospasm, coronary artery spasm and altered inotropy.22 ECF-A is relatively specific in its attraction for neutrophils and eosinophils to neutralize mediators by probable phagocytosis. PAF causes degradation of platelets, resulting in aggregation. Kinins and prostaglandins increase capillary permeability, resulting in edema and increased secretion by mucous membranes. Additionally, the release of

![Figure 1](https://example.com/figure1.png)

**Figure 1**

**SENSITIZATION**

1. **ANTIGEN** (ALLERGEN)
2. **EXPOSURE**
3. **LYMPHOID TISSUE**
4. **PLASMA CELL**
5. **RESPONSE**
6. **ANTIBODY** (IGE)
7. **MAST CELL**
8. **BASOPHIL**
9. **PLATELET**

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prostaglandins promotes bronchospasm and pulmonary hypertension.

It should be emphasized that the signs and symptoms of anaphylaxis can occur very rapidly. Specific signs and symptoms may initially occur alone or in various combinations. Within minutes a life-threatening situation with cardiovascular fluid shift and pulmonary dysfunction develops. The target shock organ responds with vasodilatation, increased cell wall permeability and contraction of smooth muscle.

There is some variability between individuals as to which "shock organ" is affected. The shock organ most often involved in fatal human anaphylactic reactions is often thought to be the respiratory system. Bronchial obstruction and pulmonary hyperinflation result from acute upper airway obstruction caused by angioedema of the larynx and epiglottis. The respiratory abnormalities resulting in bronchospasm and airflow limitation are similar to those observed in status asthmaticus.

Preoperative considerations and preparation

Obtaining a thorough history and physical is vital. (Table I). When a specific antigen is injected directly into the circulation, the response is widespread. In the case of chymopapain injection, certain individuals may be at special risk. Females have a six fold increased incidence of anaphylactic reaction to chymopapain. Patients who have chronic atopy (a history of allergies such as hay fever, asthma, eczema, multiple drug allergies or food sensitivities) are more likely to experience a reaction.

Patients who present with a history of congestive heart failure, coronary artery disease, or impaired cardiopulmonary physiological reserve are at greater risk if an anaphylactic reaction occurs. This is due to a reduced compensatory capacity to withstand the physiological insult of anaphylaxis and its treatment. Individuals who have been maintained on MAO inhibitors, reserpine compounds, guanethidine or other potent drugs that markedly alter normal cardiovascular physiology should not be considered candidates for chemonucleolysis. They should be reconsidered for this treatment modality only after they have been weaned off the medication in question or converted to a suitable alternative drug.

Due to the hazard of possible re-exposure once the patient has been sensitized, it is important to obtain a thorough drug history for the patient. It is vital to distinguish between a side effect (intolerance or idiosyncrasy) and an allergic response (hives, wheezing or severe hypotension). It is interesting to note that chymopapain is present in some charcoal-activated digestant preparations suggested for complaints of flatulence, indigestion and diarrhea, and it is also an ingredient in some meat tenderizers. (See Herriotts in this issue.) It is possible that a large number of our population has been exposed to chymopapain orally due to

Figure 2

ANAPHYLAXIS: "LOCKING"

PROSTAGLANDINS
KININS

Ca++

ECF - A

Mg++

SEROTONIN

MAST CELL

HISTAMINE

SRS - A

PAF
Figure 3
MEDIATORS OF ANAPHYLAXIS

SRS-A = SLOW-REACTING SUBSTANCE OF ANAPHYLAXIS
PAF = PLATELET AGGREGATING FACTOR
ECF-A = EOSINOPHIL CHEMOTACTIC FACTOR OF ANAPHYLAXIS

SRS-A

CONTRACTION
SMOOTH
MUSCLE

BRONCHOSPASM

CORONARY
ARTERY
SPASM

HISTAMINE

VASODILATION

HYPOTENSION

INCREASED
CAPILLARY AND VENULE
PERMEABILITY

EDEMA

INCREASED
SECRETIONS

PAF

DEGRANULATION
OF PLATELETS

AGGREGATION

ECF-A

NEUTRALIZORS
MEDIATORS

PHAGOCYTOSIS

KININS
PROSTAGLANDINS
prevalence of products containing this enzyme. This type of exposure may or may not sensitize the individual to the intradiscal injection of chymopapain. Presently there are no reliable skin tests to determine which patients will be susceptible to chymopapain induced anaphylaxis.\textsuperscript{18} Cymopapain is a foreign protein and its injection has the potential for generating an immunological response. Therefore, patients who have already received an injection of any form of chymopapain should not be reinjected with the enzyme.\textsuperscript{28} (See Addendum for more up-to-date testing information.)

Any individual receiving beta adrenergic blockers to treat cardiovascular and other disorders such as hypertension, angina pectoris, cardiac arrhythmias, hyperthyroidism, anxiety states, migraine headaches or pheochromocytoma should be closely monitored. Additional monitoring may include the use of a direct indwelling arterial line for rapid and reliable blood pressure and blood gas determination. CVP monitoring can be utilized to guide fluid management. The use of a Swan Ganz\textsuperscript{TM} pulmonary artery catheter may be helpful in certain isolated situations in which patients have a moderate degree of left heart dysfunction. (Although if the condition of the patient warrants the use of this monitoring device, his or her suitability as a chemonucleolysis candidate should be seriously questioned.)

It should be emphasized that chemonucleolysis should not be viewed as an alternative to lumbar laminectomy in high risk patients. To the contrary: the authors believe high risk patients would tolerate lumbar laminectomy more readily than a possible anaphylactic reaction from a chemonucleolysis procedure. Each candidate’s suitability for

<table>
<thead>
<tr>
<th>Table I: Preoperative recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain history</td>
</tr>
<tr>
<td>Females 6:1 incidence—particularly with an elevated erythrocyte sedimentation rate.\textsuperscript{18, 27}</td>
</tr>
<tr>
<td>Known hypersensitivity—atopic individuals—increased incidence of allergic reactions.</td>
</tr>
<tr>
<td>May require special monitoring—possibly arterial line, CVP and/or Swan Ganz\textsuperscript{TM} tailored to individual patient history:</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Cardiovascular dysfunction</td>
</tr>
<tr>
<td>Beta blockers.</td>
</tr>
<tr>
<td>Patients that have had previous injections of chymopapain should not be reinjected (first injection may have sensitized them to subsequent injections of the enzyme).</td>
</tr>
<tr>
<td>Drug history: Exclude patients with history of prior anaphylactic reactions, known sensitivity to papaya and derivatives and known sensitivity to iodine or iodine contrast material.\textsuperscript{18}</td>
</tr>
<tr>
<td>Patients receiving MAO inhibitors, reserpine compounds, guanethidine or other drugs that markedly alter cardiovascular physiology are not suitable candidates while they are maintained on these agents.</td>
</tr>
<tr>
<td>Preloading</td>
</tr>
<tr>
<td>12-15 ml/kg D$_5$/RL</td>
</tr>
<tr>
<td>—Large bore IV catheter</td>
</tr>
<tr>
<td>H$_1$ Blockers</td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl\textsuperscript{®})</td>
</tr>
<tr>
<td>—1 mg/kg q 6 hours po for 24 hours prior to chemonucleolysis</td>
</tr>
<tr>
<td>H$_2$ Blockers</td>
</tr>
<tr>
<td>Cimetidine (Tagamet\textsuperscript{®})</td>
</tr>
<tr>
<td>—4 mg/kg q 6 hours po for 24 hours prior to chemonucleolysis</td>
</tr>
<tr>
<td>Steroids (optional)</td>
</tr>
<tr>
<td>Cortisol (Solu-Cortef\textsuperscript{®})</td>
</tr>
<tr>
<td>—1 gm IV or po administered day before chemonucleolysis</td>
</tr>
</tbody>
</table>
chymopapain injection should be evaluated in light of estimations of how well the patient would tolerate the rigors of anaphylaxis and its treatment.

Beta blockers inhibit the sympathetic actions of beta receptors by competing with the catecholamines, thereby blocking cardiac acceleration at the receptor site. The beta blocking action also causes inhibition of both cardiac output and bronchial dilatation. One of the most important responses to beta blockade outside of the cardiovascular system is performed by the bronchi and bronchioles. Bronchodilation is a beta_2 adrenergic response. It is significant that beta_2 selective blockers or non-specific beta blockers can potentiate bronchospasm, since bronchospasm is a cardinal sign observed in anaphylaxis. Beta adrenergic agents augment cyclic adenosine 3’: 5’-monophosphate (cyclic AMP) production, decreasing the availability of mediators for release.

Cyclic AMP is involved in both mast cell degranulation and in smooth muscle contraction. Agents that elevate intracellular cyclic AMP inhibit both processes, and thus help abort the anaphylactic reactions. Investigators have demonstrated that beta blockers, like propranolol, block the “antianaphylactic” effect of catecholamines on antigen-induced histamine release from the sensitized lung. In addition, circulatory eosinophils increase in humans during the administration of propranolol, and the reduction characteristically induced by epinephrine is blocked.

Preoperative preparation with steroids is somewhat controversial. The preoperative use of steroids may be reserved for those patients considered to be at greater than ordinary risk of having a reaction. In any event, it is believed that hydrocortisone sodium succinate 1 gm PO or IV will stabilize cell membranes and decrease membrane permeability. It has been demonstrated that 30% of patients undergoing chemonucleolysis develop severe backaches of usually several hours duration. Preoperative steroids can frequently reduce this pain. It has been hypothesized that steroids help preserve the integrity of capillary membranes, prevent aggregation of red cells, and preserve the metabolic activities of the cell membrane. Because acute hypersensitive reactions cannot be aborted with steroids, some investigators argue against the routine use of this class of drugs.

Until recently, preoperative antihistamine use was limited to H_1-receptor antagonists. Now H_1—receptor antagonists are being used in conjunction with H_2—receptor antagonists. Traditionally, histamine receptors have been categorized as classical (or H_1) receptors and gastric (or H_2) receptors. It is now thought that both H_1 and H_2 receptors may exist in the myocardium, the vasculature, and the respiratory system.

The role of H_1 and H_2 receptors in the cardiovascular system forms the basis for the use of H_1 and H_2 receptor antagonists for prophylaxis against anaphylactic reactions. Systemic vascular resistance is the most direct hemodynamic measurement of histamine release, but hypotension and tachycardia are the clinical signs most commonly observed. Some investigators feel that H_2 receptors may be analogous to B-adrenergic receptors. Animal experiments suggest that the initial phase of histamine-induced hypotension may be H_1 mediated, and the prolonged hypotension may be H_2 mediated.

Studies with human heart transplant material suggest that H_1 receptors may mediate coronary artery vasodilatation. H_2 receptor stimulation in the myocardium may cause increased inotropy and chronotropy, although the role of this finding in the normal patient is not known. Rapid intravenous infusions of large doses of cimetidine have caused life-threatening arrhythmias and profound hypotension in critically ill patients. Likewise, H_1 receptor stimulation may cause negative inotropic effects.

At any rate, several studies have shown that both H_1 and H_2 blockers must be given to significantly block cardiovascular response to histamine. Furthermore, analysis of the data demonstrates no interaction between the H_1 and H_2 receptors in the cardiovascular system—that is, they mediate their effects independently. One study showed that the intravenous infusion of both cimetidine (4 mg/kg) and diphenhydramine (1 mg/kg) 15 minutes before administration of an investigational neuromuscular blocking agent significantly blocked the cardiovascular response to the agent’s histamine release. Philbin demonstrated that in four groups of patients receiving either a placebo, H_1 antagonist, H_2 antagonist or both H_1 and H_2 antagonists, only the group receiving both H_1 and H_2 antagonists showed no change in systemic vascular resistance after administration of morphine sulfate.

There has been some hesitation about using H_2 receptor antagonists in asthmatics, the idea being that there may be an imbalance of H_1 and H_2 receptors in the respiratory systems of asthmatics and that H_1 receptors are responsible for bronchoconstriction and H_2 receptors are responsible for bronchodilation. The role of histamine in an asthmatic attack, however, is not clear. Serum histamine levels are not raised during an attack.
and antihistamines are not effective in treating asthma. Slow reacting substance of anaphylaxis is a potent bronchoconstrictor and acts even in the presence of antihistamines.

As mentioned previously, data suggest that \( H_1 \) and \( H_2 \) receptors function independently. It will be interesting to see, however, what the future role for more potent and specific \( H_2 \) receptors, such as ranitidine and SKF 93479, will be with regard to allergy prophylaxis. These agents could further differentiate the roles of \( H_1 \) and \( H_2 \) receptors.

In summary, histamine is probably the most important mediator of anaphylactic/anaphylactoid reactions. The competitive inhibition of both \( H_1 \) and \( H_2 \) receptors by \( H_1 \) and \( H_2 \) receptor antagonists with prophylactic use of agents such as diphenhydramine and cimetidine has been shown to significantly attenuate much of the cardiovascular response to histamine release.

### Anesthetic technique

During the initial controlled studies conducted according to FDA guidelines, only local anesthesia with sedation could be utilized. This was done to reduce the variables in determining the etiology of anaphylactic reactions.

Chemonucleolysis has been performed successfully with general and local anesthesia techniques. Although this is still an area of controversy, many anesthesia practitioners now believe that general anesthesia with tracheal intubation is superior to local anesthesia for chemonucleolysis. In practice, most investigators have used general anesthesia with intubation before intradiscal placement of needles for the administration of chymopapain.

General anesthesia with tracheal intubation enables the anesthesia practitioner to respond rapidly in the event of an anaphylactic reaction.

In addition, the authors believe the procedure is too long and painful to be performed under local anesthesia. Having been counseled about the possibility of an anaphylactic reaction, patients also are generally too anxious to tolerate the procedure under local anesthesia.

The patient is placed in a lateral decubitus position with elevation of the flank (similar to an elevated kidney rest position). Several factors add to the overall time of the procedure. These factors include: fluoroscopy for needle placement, discography with radiopaque iodine-based dye (to assist in determining the integrity of the disc), an allowance of at least 15 minutes elapsed time to allow for diffusion or absorption of the dye before injection of the enzyme (this also allows for observation of possible allergic reaction to contrast material), a test dose of chymopapain with a 20-minute post-injection observation period for possible reaction, and finally the injection of the therapeutic dose of the enzyme with another 20 minute period for observation before the anesthesia is discontinued and the patient is extubated. In addition, because this is a new procedure, surgeons generally will take longer until they become more familiar with the technique.

Intubation of the trachea may become impossible due to laryngeal edema once an anaphylactic reaction occurs. In contrast, intubation can usually be readily performed immediately after induction of general anesthesia, thus saving valuable time that would otherwise be used to establish an airway during a potentially life-threatening anaphylactic reaction. Probably the most important reason that routine intubation should be performed immediately after induction of anesthesia is prevention of aspiration. In one large series of disc injections with chymopapain, the only complications reported were three cases of aspiration pneumonia. These were attributed to intubations performed in the lateral decubitus position. These intubations were not performed in response to allergic reactions, as no allergic complications were observed in the series.

A large well-placed plastic intravenous cannula is mandatory. This provides access to the cardiovascular system, enabling rapid peak blood levels of drugs administered and the potential for rapid infusion of intravenous fluids.

Fluid preloading of 12-15 ml/kg of body weight is recommended prior to induction of anesthesia. The first liter of fluid should consist of Ringer’s lactate with 5% dextrose followed by plain Ringer’s lactate. Preloading provides greater reaction time to treat patients who have massive fluid shifts from the intravascular space during an anaphylactic reaction. It is estimated that a 1 mm layer of subcutaneous fluid over the surface area of an average adult body would represent a reduction in intravascular fluid volume of 1.5 liters. Therefore, it can be reasoned that massive fluid shifts that occur during anaphylaxis could represent several liters of fluid.

Some investigators believe potent volatile inhalational agents should be avoided because of undesired reduction of systemic vascular resistance (SVR) and cardiac depression (negative inotropy). Others see reduction of the SVR as beneficial in that it allows for greater vasodilation in order to enhance fluid infusion. If an agent like isoflurane is used initially to reduce the SVR, it should be discontinued for a minimum of 5 to 5 minutes.
prior to the chymopapain injection to reduce its negative inotropic effect. In a national anesthesia panel discussion\textsuperscript{17} on the subject, Dr. R. T. Myers stated that in the event of a reaction “a strong heart is needed to pump the extra fluid, and in an overwhelming reaction, I think cardiovascular depression is very important. We can give fluids and medicine, but if the pump is weak, we will be in trouble.” In the same discussion Dr. L. C. Beck succinctly stated, “I avoid the myocardial depressants.”

Because the use of epinephrine is mandatory in the treatment of anaphylaxis, halothane should be avoided to prevent potentially lethal cardiac rhythm disturbances.\textsuperscript{36,39} Additionally, known histamine-releasing drugs such as d-Tubocurarine and morphine should be avoided.

The authors believe that a balanced anesthetic technique utilizing \textsubscript{N}_{2}O\textsubscript{2}O\textsubscript{2} and intravenous agents is the most cardiovascularly stable approach that can be employed for chemonucleolysis. In addition, the authors believe endotracheal intubation prior to chymopapain injection in the lateral position is essential.

Induction is generally performed with sodium thiopental (3-4 mg/kg). Intubation is facilitated by the use of a succinylcholine bolus (1 mg/kg). Fentanyl (1-2 \textmu g/kg) is used to provide analgesia. Light muscle relaxation can be provided by the use of a succinylcholine drip (0.1-0.2\%) or by pancuronium (Pavulon\textsuperscript{8}) or dimethyl tubocurarine iodide (Metubine\textsuperscript{8}). These relaxants have little to no histamine release in usual clinical doses.

Fentanyl provides good short term analgesia while preserving cardiovascular stability due to its limited effect on SVR, coronary blood flow, and ventricular function. Droperidol, on the other hand, should be avoided because of inconsistent effects on hemodynamics due to its alpha-blockade characteristics.\textsuperscript{40} Valium in small increments of 2.5 mg (up to a total of 5 mg) prior to induction will help allay anxiety and reduce the needed dose of sodium thiopental.

The authors have not found hypertension to be a significant problem when a well-conducted, balanced technique for general anesthesia is employed, although occasionally, hypertension occurs to the degree that it requires intervention. A commonly utilized method of intervention involves the careful titration of hydralazine alone or in combination with propranolol. Because these drugs act to reduce arterial blood pressure by arteriolar vasodilatation and beta adrenergic blockade, their use for treating hypertension during anesthesia for chemonucleolysis could be hazardous. The relatively long half-life of these drugs could cause sustained vasodilatation, decreased heart rate and decreased cardiac contractility. This state would render epinephrine less effective in combating the effects of anaphylaxis.

The authors’ recommendation for treatment of hypertension in this circumstance would be to deepen the anesthesia. This usually can be achieved with the addition of one or more increment doses of 50-75 mg of sodium thiopental and 50-150 \mu g of fentanyl. If this proves insufficient, a low concentration of isoflurane could be employed for its peripheral vasodilating effect. It should be remembered that isoflurane should be discontinued for a minimum of 3-5 minutes prior to the chymopapain injection to minimize any negative inotropic effects.

A test dose of chymopapain is given to reduce the antigen dosage in the event a reaction occurs. If no reaction occurs in 20 minutes after the test dose, a full dose of 1-2 ml is injected. Careful monitoring of vital signs and electrocardiogram is essential in early detection of adverse reactions to the chymopapain injection.

An anaphylactic reaction is most likely to occur within the first 20 minutes following injection, although the possibility of an anaphylactic reaction is still high during the initial 21\frac{1}{2} hours postinjection. Early signs may appear insignificant but could be the precursors of a full anaphylactic reaction. Signs of a reaction may include a fall in blood pressure, change in heart rate, bronchospasm, piloerection, erythema, and/or urticaria.

In the authors’ institution, a kit of anticipated medications is maintained in the surgical room where the procedure is performed. Certain key medications are maintained in prefilled syringes ready for rapid administration. The kit is sent with the patient to the recovery room to be readily available if a late reaction occurs (Table III). All surgery and recovery personnel should be aware of the hazards associated with chemonucleolysis. It is desirable to make specific assignments for involved personnel to carry out the anaphylaxis treatment protocol.

Management of anaphylaxis

Anticipation, early recognition and proper treatment of an anaphylactic reaction are goals of management. The course of anaphylaxis cannot always be predicted. The anesthesia practitioner should be aware of the life-threatening signs of respiratory failure and circulatory shock. The signs of anaphylaxis can vary from mild generalized pruritus to irreversible cardiovascular shock or fatal pulmonary insufficiency (Figures 4 and 5).
For the majority of patients, careful physiologic monitoring and a well-planned protocol of treatment have proven to be effective in managing anaphylactic reactions. (Table II.) Initiation of appropriate therapy early in the course of a reaction is of paramount importance. The basis for treatment centers on maintenance of adequate circulation and proper oxygenation.

Initial therapy should include the termination of the chymopapain injection and maintenance of an airway with the administration of 100% O2 through an endotracheal tube while discontinuing all anesthetic agents. Positive pressure oxygen therapy should be instituted because hypoxemia increases pulmonary artery pressure. High concentrations of oxygen may reduce right ventricular strain once the hypoxemia is eliminated, allowing a decrease in pulmonary artery pressure.

### Table II
Protocol for management of anaphylaxis with available resuscitation drugs

<table>
<thead>
<tr>
<th>Terminate injection</th>
<th>Administer 100% oxygen</th>
<th>Discontinue all anesthetic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer epinephrine (Adrenalin®)—initial therapy drug of choice</td>
<td>—0.05–0.1 mg IV titrated to treat hypotension</td>
<td>—0.1–0.5 mg IV for cardiovascular collapse</td>
</tr>
<tr>
<td>—IV infusion—2 to 20 µg/min—for sustained effect</td>
<td>Rapid volume expansion with crystalloids and/or colloids²⁰</td>
<td></td>
</tr>
<tr>
<td>—10–25 ml/kg</td>
<td>Insure adequate oxygenation and circulation</td>
<td></td>
</tr>
</tbody>
</table>

—closed chest cardiac compression if necessary

**Adjunctive therapy: Following initial therapy with epinephrine**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug and recommended dosage range</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-adrenergics</td>
<td>Isoproterenol (Isuprel®) 1-4 µg/min IV infusion</td>
<td>Refractory bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Dopamine 1-15 µg/kg/min IV infusion (mixed beta and alpha effect—recommended dosage is predominately in beta range)</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal to slow heart rate</td>
</tr>
<tr>
<td>Alpha-adrenergics</td>
<td>Noradrenaline (Levophed®) 1-15 µg/min IV infusion</td>
<td>Refractory hypotension</td>
</tr>
<tr>
<td></td>
<td>Metaraminol (Aramine®) 0.5–2.0 mg IV bolus</td>
<td>with tachycardia</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Aminophylline 7-9 mg/kg IV infusion over 20–30 min</td>
<td>Refractory hypotension with tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent bronchospasm</td>
</tr>
<tr>
<td>H1 Blockers</td>
<td>Diphenhydramine (Benadryl®) 0.5–1.0 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>H2 Blockers</td>
<td>Cimetidine (Tagamet®) 4 mg/kg IV over 15–30 min</td>
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</tr>
<tr>
<td>Steroids</td>
<td>Cortisol (Solu-Cortef®) 1 gm IV</td>
<td></td>
</tr>
<tr>
<td>Acid-base balance</td>
<td>Sodium bicarbonate 50–100 mEq prn ABG’s</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4
ANAPHYLAXIS: CIRCULATORY SHOCK

**Vasodilation**

**Antigen - Antibody "locking"**

**Histamine and other mediators of anaphylaxis**

**Hypotension**

**Reduction in cardiac output**

**Decreased preload**

**Vasoconstriction**

**Platelet aggregation**

**Reduced blood flow**

**Capillary stasis**

**Acidosis**

**Tissue hypoxia**

**Plasma leakage (tissue edema)**

**Decreased smooth muscle function**

**Succession of pathophysiological circulatory occurrences during anaphylaxis**
Figure 5

ANAPHYLAXIS: PULMONARY INSUFFICIENCY

ANTIGEN - ANTIBODY "LOCKING"

CONTRACTION SMOOTH MUSCLE

BRONCHOSPASM

DECREASED PERFUSION

RETENTION CARBON DIOXIDE

TACHYPNEA

HYPOXEMIA

INCREASED CAPILLARY PERMEABILITY

EDEMA

INCREASED SECRETIONS

INCREASED PULMONARY VASCULAR RESISTANCE

ATELECTASIS

SUCCESSION OF PATHOPHYSIOLOGICAL PULMONARY OCCURRENCES DURING ANAPHYLAXIS
The cardiovascular manifestations, highlighted by hypotension, can be attributed to the increased permeability of vessels with the resultant loss of plasma from the intravascular space. Due to these massive fluid shifts, the intravascular volume must be restored by the rapid administration of intravenous fluids in the range of 10-25 ml/kg. In the normal state, the venous side of the circulation serves as the capacitance vessels—however, in cardiovascular shock the microcirculation capacity is increased. The total capacity of the microcirculation is approximately 500 times the total blood volume.

In addition to hypotension, the patient may present with sudden severe bronchospasm, making ventilation impossible. The initial concern is to treat the hypotension and bronchospasm. Epinephrine remains the drug of choice to relieve the multiple effects of anaphylaxis.\(^2\) Epinephrine is a sympathomimetic with both alpha and beta agonist activity.

Death from an anaphylactic reaction is primarily a direct result of severe hypotension, bronchospasm and/or edema of the upper airway. Epinephrine helps attenuate all these events. Epinephrine decreases the life-threatening suffocation from edema of the glottis. It additionally relaxes the bronchial smooth muscle by virtue of its beta-adrenergic stimulating effect. The mixed alpha and beta effects increase cardiac output and the SVR, thereby restoring adequate blood pressure for improved perfusion. Inadequate ventilation adds to the acidosis of shock, hypoxemia of pooled blood, and poor ventilation-perfusion ratios in the lung. Moderate hyperventilation should be utilized once a reaction occurs to improve oxygenation and acid-base status.

Epinephrine initiates vasoconstriction to combat the vasodilatation and hypotension caused by histamine release. In addition to stimulating alpha and beta adrenergic receptors, adenyl cyclase activity is potentiates, increasing cyclic AMP in the tissues which acts to inhibit the release of mediators. Initially an intravenous bolus of epinephrine 0.05-0.10 mg (0.5-1.0 cc of 1:10,000 solution), titrated to restore adequate blood pressure, is recommended. A dilute intravenous infusion of 2-20 \(\mu\)g/min can be initiated, or incremental doses of up to 0.3 mg IV can be repeated every 15-20 minutes as necessary. To reduce dysrhythmias, excessive rises in blood pressure and other side effects, the epinephrine dosage that is administered should be closely titrated. Administration of the minimal dose needed to achieve the desired effect should be the goal of therapy. If the desired response is not achieved, the epinephrine can be repeated. The effects of epinephrine are rapid but short-lived, and the dosage often needs to be repeated.

Specific beta adrenergics can also be employed in patients who have persistent bronchospasm and are hemodynamically stable. An infusion of isoproterenol (Isuprel\(^8\)) 1-4 \(\mu\)g/min may be employed. Isoproterenol has a shorter duration than epinephrine.\(^9\) Isoproterenol lowers peripheral vascular resistance through its beta\(_2\)-adrenergic effect, and therefore should be used with caution in the presence of hypotension and/or hypovolemia.\(^17,20,29\)

Ephedrine stimulates alpha and beta adrenergic receptors, causing vasoconstriction, bronchodilation and increased myocardial contractility. Ephedrine should never be utilized in place of epinephrine in the treatment of acute anaphylaxis. It should be emphasized that epinephrine should remain the drug of choice in treatment of anaphylactic reaction.\(^17,22\)

In the course of shock, there is an initial outpouring of endogenous catecholamines resulting in vasoconstriction which continues until shortly before death. This shifts blood from vital organs to the coronary and cerebral vessels. In typical anaphylactic reactions, the systemic vascular resistance is decreased. In order to maintain an adequate blood pressure, peripheral vasoconstrictors are often required. An infusion of norepinephrine (Levophed\(^8\)) 1-15 \(\mu\)g/min, or metaraminol (Aramine\(^8\)) 0.5-2.0 mg IV bolus, can be employed. Care must be taken to titrate vasopressors closely to avoid an excessive rebound increase in blood pressure which can lead to increased myocardial oxygen demand.

Other organs, primarily the kidneys, can also be greatly compromised. The body's intrinsic release of vasoconstrictors mediated by the sympathetic nervous system may only further compromise blood flow. The importance of adequate volume loading in conjunction with sympathomimetic agents is vital to maintain coronary and cerebral circulation as well as renal perfusion. The use of dopamine in low or intermediate dosages (1-15 mg/kg/min) exerts a positive inotropic effect on the myocardium while reducing regional arterial resistance in the mesentery and the kidneys.\(^27\) This dopaminergic effect is associated with an increase in glomerular filtration rate, renal blood flow, and sodium excretion. Because dopamine has a positive chronotropic effect, it is best utilized in patients with normal to slow cardiac rates.

Glucocorticoids can be employed as a supplement to definitive therapy. Steroids are believed to act by enhancing the effect of epinephrine on ad-
enyl cyclase, and they seem to interfere with histamine release. However, since their effects take time to develop, preoperative utilization is needed to gain maximum benefit. Steroids suppress the inflammatory process as a result of increased capillary permeability. The action of corticosteroids is believed to produce an alteration of tissue reactivity to an antigen, thereby suppressing the inflammatory response.

Aminophylline, a phosphodiesterase inhibitor, should be administered to treat severe or sustained bronchospasm. Methylxanthines such as aminophylline promote bronchodilation by an increasing level of cAMP. Phosphodiesterase, the enzyme that breaks down cAMP, is inhibited by methylxanthines, thereby increasing cAMP levels. The increased cAMP levels will in turn inhibit the release of mediators. In addition to relieving bronchospasm by relaxing smooth muscle, aminophylline tends to increase cardiac output. Like all methylxanthine bronchodilators, aminophylline can induce arrhythmias. A recommended dose of aminophylline is 7.9 mg/kg to be administered by intravenous infusion over 20-30 minutes. An intravenous drip of aminophylline 500 mg diluted in 250 ml of 5% dextrose is generally utilized.

Diphenhydramine 0.5-1.0 mg/kg and cimetidine 4 mg/kg should be given intravenously to help block the cardiovascular response to histamine release. These H$_1$ and H$_2$ blockers act by competitive inhibition of histamine at target cells.

The pathological alteration of the airways sets the stage for respiratory acidosis. The situation presents itself following inadequate ventilation with resultant retention of carbon dioxide. The lungs are frequently unable to compensate for the disturbance, as they are one of the disabled shock organs. Respiratory and/or metabolic acidosis should be treated directly until the shock organ begins to recover. This can be accomplished by the intravenous injection of sodium bicarbonate as needed based upon blood gas results. A 50 mEq ampule of sodium bicarbonate should be administered empirically every 5 minutes for severe hypotension until blood gas results are obtained. Upon correction of acid-base disturbances, the bronchodilating and vasoactive drugs will be more effective.

Theoretically, anticholinergic drugs like atropine would reduce cellular release of mediators by decreasing intracellular concentrations of guanosine monophosphate. The inhibitory parasympathetic effects on the cardiovascular system are also eliminated. If the use of atropine appears to be indicated, it may be given in small intravenous increments of 0.4-0.5 mg.

The use of calcium for its positive inotropic effect is probably relatively contraindicated in view of present medical knowledge. The mast cells function in a calcium energy-dependent process. Substantial data suggests that migration of calcium into mast cells is necessary for the degranulation process that causes release of mediators. The use of calcium would also add to the potent coronary vasoconstrictive effect of slow-reacting substances of anaphylaxis.

A chest x-ray should be obtained to evaluate laryngeal edema. Laryngoscopy should be performed prior to extubation to further evaluate possible residual laryngeal edema.

It is important to be aware that pharmacologic mediators are released for up to 48 hours after the initial reaction. Effective treatment of clinical manifestations of anaphylaxis requires that drugs be readily available so that the proper pharmacological intervention can be carried out. It is suggested that the drug treatment box accompany the patient to the recovery room or intensive care unit. It is possible that a late reaction may occur within 2½ hours after chymopapain injection, and if it does, the drugs will be readily available for use. It would seem prudent to maintain an intravenous line for at least 24 hours after chemonucleolysis. This would facilitate prompt treatment of any late reactions.

**Discussion**

Severe allergic reactions are possible during the course of any anesthetic administration. The cause, recognition and treatment of anaphylactic reactions after the injection of chymopapain have been presented. The anesthesia provider should be cognizant of the fact that severe allergic reactions can be caused by a variety of other agents. A partial list would include intravenous anesthetic agents (barbiturates, etomidate, narcotics and others), iodinated radiographic contrast media, antibiotics, local anesthetics, muscle relaxants, protamine, blood, plasma and plasma substitutes.

The pathophysiology of any severe systemic allergic reaction and its treatment would be similar to that presented for chymopapain reactions. An understanding of the concepts presented here should provide the basis for treatment of any severe allergic reaction occurring during anesthesia for any type of surgical procedure. As in any critical situation, treatment must be tailored to the particular patient and circumstances.

Unfortunately, the conclusion of several in-
vestigators is disturbing: "There may be no ideal therapy for severe anaphylaxis even under optimal conditions." It is because of this conclusion that anaphylaxis treatment protocols are subject to change. As new research is conducted and pharmacological agents are developed, treatment approaches to anaphylactic reactions will undoubtedly be revised and improved.

Conclusion

The management of anesthesia for patients undergoing chemonucleolysis should be well planned. With the reported 1% incidence of anaphylactic reactions, the anesthetist should have a clear understanding of the mechanism of anaphylaxis and a proper treatment protocol at hand.

Addendum

Recently, a laboratory test has been developed that has shown a high degree of accuracy in predicting those patients who will possibly react to chymopapain. The test is marketed as ChymoFAST™ by Smith Laboratories. This test, which is an enzyme immunofluorescent assay, is conducted essentially by reacting chymopapain with a sample of the patient’s serum. To date, the predictive value of a negative result in patients selected for chymopapain injection is 99.8%. The predictive value of a positive result is 64%. This latter figure is affected by the understandable reluctance to inject with chymopapain those patients who show positive results to the ChymoFAST™ test.

REFERENCES

(43) Personal communication with Barry Crispin, MT (ASCP), MS. May, 1984. Allergenetics Reference Laboratory, Mountain View, California.
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Acknowledgement

The authors wish to express their gratitude to Barbara Johnson, Patricia Keyser, Lori Chasar, Brenda Brown and Ollie Ward for their assistance in the preparation of this manuscript, and to Karen L. Snyder and the staff of Aultman Hospital Media Center for assistance with the graphics. Additionally, the authors wish to thank the following orthopedic surgeons for their support and cooperation in developing a protocol for the anesthetic and surgical management of chemonucleolysis at Aultman Hospital: Robert Manns, MD; Paul Welch, MD; Dennis Glazer, MD; and George Korte, MD.