

ANAPHYLACTIC REACTIONS TO AQUEOUS CHYMOTRYPSIN

Angelo Ferrara, M.D., Stanley R. Finke, M.D.,* Michael H. Grieco, M.D.,*
John T. Connell, M.D.,** and William B. Sherman, M.D.,*** New York City, N. Y.*

PROTEOLYTIC enzymes are now used as adjunct therapy in the treatment of many diseases. One of the more frequently used of these preparations is chymotrypsin, available in oral, topical, and parenteral forms. Aqueous chymotrypsin† is a proteolytic enzyme extracted from beef pancreas and is a stable solution of purified chymotrypsin. The injectable material contains 5,000 Armour units (0.7 mg. of protein nitrogen) of chymotrypsin per milliliter in 0.9 per cent sodium chloride, 0.2 per cent calcium acetate, and 0.01 per cent thimerosal. This enzyme has been classified as an endopeptidase because of its activity in splitting peptide linkages which are not close to free amino or carboxyl groups.

This enzyme is said by the manufacturer to reduce and prevent local inflammation, edema, and effusion of blood and lymph. It is recommended for the treatment of thrombophlebitis, peptic ulcer, injuries, dental hematomas, and other conditions.

The manufacturer states that allergic reactions to chymotrypsin are uncommon. We present in this communication 2 case reports which illustrate immediate generalized reactions to the parenteral administration of aqueous chymotrypsin.

CASE REPORTS

CASE 1—I. J., a 44-year-old white woman, was admitted to The Roosevelt Hospital on Aug. 19, 1962, with angioedema and urticaria after the intramuscular injection of aqueous chymotrypsin. The patient had a history of active peptic ulcer for 20 years which had been treated with diet and oral medications. There was no past history of eczema, allergic rhinitis, bronchial asthma, or drug allergies. About 10 months prior to this admission, the patient had received 8 daily intramuscular injections of 5,000 Armour proteolytic units of aqueous chymotrypsin for epigastric pain, with some relief of symptoms. On the day of admission, epigastric pain recurred and the patient received an intramuscular injection of

From the Institute of Allergy, The Roosevelt Hospital, New York City, N. Y.

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*Resident, Institute of Allergy, The Roosevelt Hospital.

**Assistant Attending Allergy; Educational Coordinator The Institute of Allergy, The Roosevelt Hospital.

***Director, Institute of Allergy, The Roosevelt Hospital; Associate Clinical Professor of Medicine, Columbia University.

†Kindly supplied as Chymar Aqueous by Armour Pharmaceutical Co., Kankakee, Ill.

5,000 units of aqueous chymotrypsin from her private physician. One-half hour after this injection the patient noted itching of the palms, edema of the face, lightheadedness, and difficulty in speaking. Injections of 1 ml. of aqueous epinephrine 1-1000 (subcutaneously), 10 mg. diphenhydramine hydrochloride (intramuscularly), and 40 units ACTH gel (intramuscularly) were immediately given after which the patient was sent to The Roosevelt Hospital emergency room. Injections of epinephrine and diphenhydramine were repeated and the patient was admitted to the hospital.

Physical examination showed the blood pressure to be 100/80 mm. Hg and the pulse 108 a minute. Respirations were regular and not labored. The significant findings were epigastric tenderness on abdominal palpation and diffuse edema of the face, tongue, and eyelids. There was a maculopapular rash on the lower extremities. The patient was given antihistamines and discharged within 24 hours completely free of symptoms. The result of immunologic studies of this patient are presented in Table I.

TABLE I. IMMUNOLOGICAL DATA

PATIENT AND DATE	DIRECT SKIN TEST*		PRAUSNITZ- KÜSTNER REACTION	PASSIVE CUTANEOUS ANAPHYLAXIS†	PRECIPITIN TESTS	
	500 U./ML.	50 U./ML.	500 U./ML. (0.025 ML. IN- TRADERMALLY)	SERUM DILU- TION OF 1-5	AGAR GEL DIFFUSION‡	QUALITATIVE PRECIPITIN TEST
I. J.						
Aug. 20, 1962	—	—	1 plus	0	0	0
Dec. 14, 1962	4 plus	3 plus	2 plus	0	0	0
H. B.						
Dec. 14, 1962	3 plus	2 plus	1 plus	0	0	0
Human Control	0	0	0	0	0	0
Rabbit immunized with chy- motrypsin§	—	—	—	Positive	Positive	Positive

*0.01 ml. of aqueous chymotrypsin was injected intradermally. Readings were made at 20 minutes using the criteria of Sherman and Kessler.¹³

†Performed by the method of Ovary and Blozzi.¹⁴ The challenging dose of antigen, 2 500 units of aqueous chymotrypsin, was mixed with 0.25 ml. per 100 grams of body weight (guinea pig) of 1 per cent Evans blue solution just prior to injection.

‡Ouchterlony plate method.¹⁵ Undiluted sera were tested against serial dilutions of aqueous chymotrypsin ranging from 5,000 to 20 Armour proteolytic units per milliliter.

§A gray New Zealand rabbit was immunized with three weekly parenteral injections of 2,500 units of an aqueous solution of crystalline chymotrypsin emulsified with incomplete Freund's adjuvant.

CASE 2—H. B., a 67-year-old white man, had had a left saphenous vein ligation in 1959 for thrombophlebitis. This was followed by local edema in the same extremity. The patient gave no past history of eczema, allergic rhinitis, or bronchial asthma, but stated he had a systemic reaction to a penicillin injection in 1958. In 1962 the patient developed thrombophlebitis in the right lower extremity for which he was given daily intramuscular injections of 5,000 units of aqueous chymotrypsin by his private physician. On Jan. 23, 1962, 10 minutes after the fourth injection he had angioedema and erythema of the face, together with moderate dyspnea. He was immediately given 0.5 ml. of aqueous epinephrine 1-1000 (subcutaneously), 10 mg. diphenhydramine hydrochloride (intramuscularly), and 40 mg. of methylprednisolone sodium succinate (intravenously). Recovery was prompt and the patient was sent home. The results of immunological studies are given in Table I.

DISCUSSION

Chymotrypsin is known to be a good antigen under experimental conditions.¹ The manufacturer's product brochure states that "sensitivity to chymotrypsin is uncommon." However, a review of the recent literature reveals 12 cases of anaphylactic reactions complicating intramuscular injections of chymotrypsin,²⁻¹⁰ which suggests a higher incidence of hypersensitivity than previously suspected. The 2 cases reported here raise the total number of anaphylactic reactions to 14. This is the third communication in which more than one anaphylactic reaction has been described.^{5, 7} Mozan⁹ reported 3 patients with hypersensitivity out of 78 treated with parenteral injections, one with an anaphylactic reaction and 2 with urticarial reactions. In addition, a laboratory worker developed symptoms of nasal congestion and lacrimation when handling crystalline chymotrypsin.¹¹

Howe and associates¹¹ and MacLaren and Aladjem² were able to demonstrate only skin sensitizing antibodies in patients sensitized to chymotrypsin by inhalation and the former authors inferred that the mechanism of sensitization is similar to that underlying pollen allergy. No previous immunological studies have been reported in patients sensitized by the parenteral route. In these 2 cases we have demonstrated antibodies similar to that found in the patients sensitized by inhalation, i.e., positive direct skin tests and positive Prausnitz-Küstner reactions, with negative passive cutaneous anaphylaxis and precipitin studies (Table I). These results indicate that either route of administration results in a similar immunological response to this antigen. It is still possible that precipitating antibodies are present in amounts too small to be detected by these techniques.

MacLaren and Aladjem² suggested that chymotrypsin itself could not be used for direct skin testing because of its irritative effect. We have found when using concentrations of 500 units per milliliter that no irritative phenomena occur in normal individuals. A review of those cases in which skin testing with chymotrypsin was performed following the reactions^{3, 8, 11} suggests that this procedure might be a valuable test to detect hypersensitivity prior to its clinical use.

CONCLUSIONS

The above data indicate that serious anaphylactic reactions are not infrequent sequelae to the use of chymotrypsin. In addition, an adequately controlled study demonstrating the clinical usefulness of parenteral chymotrypsin has not been reported.¹² Both of these factors should be considered by the physician prior to the use of this drug. If there is any suspicion of a patient's prior exposure to this proteolytic enzyme, skin testing with an intradermal injection of 0.01 ml. of aqueous chymotrypsin, 500 Armour proteolytic units per milliliter would appear to be wise before parenteral injection. A past history of allergic reaction to chymotrypsin should be an indication for caution in any future use of the drug.

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