

Prospective evaluation of chymopapain sensitivity in patients undergoing chemonucleolysis

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Immediate anaphylactic reactions after intradiscal chymopapain (CP) injection may occur in 1% of patients undergoing chemonucleolysis (CN). Skin prick testing to CP (10 mg/ml), a prescreening history, and CP serum-specific IgE determinations by the RAST method were performed in order to identify patients presensitized to CP before CN. Follow-up repeat CP skin testing and serum-specific IgE were done 2 to 6 weeks after CN to detect CP IgE-mediated sensitization resulting from the injection. Three of 84 patients who exhibited positive skin tests to CP before CN did not receive CP injections. Only one of the three patients (33%) was detected with elevated CP serum-specific IgE before CN. No immediate severe anaphylactic reactions caused by CP injection were encountered in the remaining 81 patients with negative CP skin tests and RASTs before CN. Eight (10%) nonlife-threatening immediate and late reactions were associated with conversion from negative skin tests and RASTs before CN to positive skin tests or RASTs after CN. Overall, 19 of 52 (37%) patients who returned for follow-up testing developed cutaneous sensitization to CP after CN. Despite the fact that RAST values after CN in these patients were significantly higher ($p < 0.002$) than those with negative skin tests after CN, the sensitivity of the RAST was only 72% for identifying patients who developed positive CP skin tests after CN. This study demonstrated that CP skin testing is essential for prescreening patients because it was more sensitive than RAST for identification of CP sensitivity both before and after CN. Late allergic reactions and cutaneous sensitization to CP were common sequelae of CN. (J ALLERGY CLIN IMMUNOL 76:458-65, 1985.)

CP, a proteolytic enzyme, has recently been approved for intradiscal dissolution of herniated lumbar discs. This procedure, CN, represents a new treatment alternative to surgical laminectomy in carefully selected patients. CP injection has been associated with an anaphylactic reaction rate of 1%, and a significant number of anaphylactic deaths had been reported before 1980.¹ This prevalence of CP-induced allergic reactions is not unexpected as sensitization to papain, a structurally related enzyme, has been described. In the workplace, inhalation of papain has been demonstrated to result in IgE-mediated occupational asthma.²⁻⁴ Oral sensitization to papain contained in meat tenderizer, health foods, and papaya juice has been well documented.⁵ Recently, we demonstrated

Abbreviations used

CP:	Chymopapain
CN:	Chemonucleolysis
PBS:	Phosphate-buffered saline
PMSF:	Phenylmethyl sulfonyl fluoride

that local ocular sensitization and angioedema may occur via exposure to papain contained in cleansing agents used for soft contact lenses.⁶ The exact prevalence of this form of ocular sensitization to papain is unknown. Current recommendations for prescreening patients before CN include a determination of serum-specific IgE against CP; however, prospective evaluation of this screening test has revealed a significant false negative rate of 42% and false positive rate of 5%.⁷ The sensitivity of serum-specific IgE compared to skin testing has not yet been evaluated. To decrease the potential severity of allergic reactions, it has been recommended that all patients be treated with H₁ and H₂ antihistamines and receive an intradiscal "test dose" of 0.2 to 0.30 ml of CP before the

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therapeutic injection. These measures have not prevented the occurrence of anaphylactic reactions immediately after the test dose.⁸ The objectives of this prospective investigation were to evaluate CP skin tests and serum-specific IgE measurements for identifying presensitized patients before CN. In addition, possible risk factors associated with CP sensitization as well as the prevalence of immediate and late allergic reactions after intradiscal injections were evaluated. Finally, cross allergenicity between CP, papain, and other protease enzymes was investigated.

METHODS

Study groups

Eighty-four patients were evaluated before undergoing intradiscal injection with CP. A careful clinical history of prior CP or papain exposure was obtained. This included questions regarding adverse responses after oral ingestion of food products containing papain such as meat tenderizer, papaya juice, and health food products. Each subject was questioned with regard to prior use of soft contact lens cleansing agents containing papain. A history of drug reactions, familial atopic diseases, and a personal history of seasonal allergic rhinitis and asthma were obtained from each patient. Follow-up histories pertaining to immediate or late adverse clinical responses associated with the procedure were obtained from each patient 2 to 6 weeks after CN. The data base form used for prescreening and follow-up is presented in Table I. Fifty-two patients returned for follow-up skin testing after the CN procedure. Two other patients (A. E. and C. G.) who were not prescreened before CN and experienced severe allergic reactions during or after the procedure were referred for immunologic evaluation after the procedure.

Immunologic studies

Skin testing. CP was diluted in PBS (pH 7.4) at a concentration of 10 mg/ml and sterilized through a 0.45 Millipore filter (Millipore Corp., Bedford, Mass.). Two other aliquots of this solution were used to prepare inactivated enzyme reagents. The first reagent was heat inactivated by boiling the CP at 100°C for 10 minutes. Chemical inactivation of the enzymatic site of the second aliquot was achieved by addition of 0.1 mmol/L of PMSF. It had been demonstrated previously that PMSF did not destroy allergenic determinants of *Bacillus subtilis* extracts used for skin testing of sensitized *B. subtilis* workers.⁹ Skin testing was performed in all patients within 48 hours of the scheduled date for CN. Previous prick test titration studies in *B. subtilis* enzyme sensitized workers in our laboratory had established that enzyme reagents, including papain at a concentration of 10 mg/ml, were reliable indicators of allergenicity in sensitized individuals without direct irritant effects in normal control subjects.⁹ CP prick tests performed at concentrations of 1 mg/ml and 10 mg/ml exhibited no significant irritant wheal responses (≥ 1 mm) in 10 nonatopic control

TABLE I. Protocol for before and after CN evaluation of chymopapain sensitivity

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|------|---|
| I. | Prescreening history |
| A. | Adverse food reactions |
| B. | Adverse reactions after ingestion of papaya food products |
| C. | Adverse response to papain lens cleansers |
| D. | History of allergic rhinitis or asthma |
| E. | Adverse reactions to other drugs |
| II. | Before CN skin prick test panel |
| A. | Chymopapain (10 mg/ml, untreated) |
| B. | Chymopapain (10 mg/ml, inactivated with PMSF) |
| C. | Chymopapain (10 mg/ml, heat inactivated) |
| D. | Saline negative control |
| E. | Histamine positive control (1 mg/ml) |
| F. | Ragweed (10 mg/ml) |
| G. | Cat dander (10 mg/ml) |
| III. | After CN follow-up |
| A. | Repeat chymopapain and control skin tests |
| B. | Description of immediate or late reactions associated with CN |
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subjects. In addition to the three CP reagents, all patients were routinely prick tested with PBS and histamine (1 mg/ml). To define objectively atopic status, two allergens, short ragweed and cat dander extracts (Hollister-Stier, Spokane, Wash.), were selected for skin testing in all patients undergoing prescreening evaluation before CN. Patients were instructed to return at time intervals ranging from 2 to 6 weeks after CN for repeat CP skin testing. A prick test with a wheal of 2 mm or greater than the saline control and a flare was considered positive. The temporal variability of reevaluation after CN was predicated only on the recuperative responses of individual patients.

Radioimmunoassay. A modified RAST was used to assay serum-specific IgE against CP in all patients before CN and was repeated in those who returned for follow-up skin testing 2 to 6 weeks later.¹⁰ Solid phase CP-bound discs were kindly supplied by Dr. Michael Sagona of Travenol Laboratories (Morton Grove, Ill.). CP (20 mg/ml) was bound to methylcellulose discs with cyanogen bromide and then washed three times successively in 1 mol/L of ethanolamine (pH 8). Sagona et al.¹¹ by use of varying concentrations of CP (5, 10, 20, and 40 mg/ml) demonstrated that optimal specific IgE binding occurred at 20 mg/ml. The test serum was then incubated with the antigen-bound discs for 14 hours and washed with PBS, followed by the addition of 35,000 cpm of ¹²⁵I-radiolabeled horse anti-human IgE. Specific IgE was expressed both as percent binding and the absolute counts per minute of ¹²⁵I-anti-IgE bound to the CP discs preincubated with the test serum. All RAST assays were performed on the same day. The counts per minute bound were converted to log₁₀ values and statistically analyzed by the Student's t test. A RAST value $\geq 1\%$ bound was considered significant and was equivalent to six standard deviations above the mean or 3.4 times more than the mean binding

TABLE II. Results of CP skin and RASTs in patients who experienced immediate and late reactions after CN

Patient	Reaction	Skin test		RAST (% Bound)	
		Before CN	After CN	Before CN	After CN
D. H.	Immediate ocular angioedema	Neg	Pos	0	1.7
D. R.	Angioedema; urticaria 2 wks after CN	Neg	Pos	0	4.7
D. L.	Angioedema; urticaria 2 wks after CN	Neg	Pos	0	16.4
B. G.	Angioedema; urticaria 10 days after CN	Neg	Pos	0	10.1
D. F.	Diffuse pruritus 1 week after CN	Neg	Pos	0	6.5
S. C.	Pruritus; hives 2 wks after CN	Neg	Pos	0	0
B. K.	Immediate rash; pruritus 1 wk after CN	Neg	Pos	0	2.2
D. L.	Urticaria 4 days after CN	Neg	Neg	0	2.7

Neg = negative; Pos = positive.

of the negative control group. A reference positive control sera obtained at 1 month and 6 months after CN from a patient (A. E.) who experienced CP anaphylaxis exhibited RAST binding of 18% and 14%, respectively. The sensitivity of the RAST assay compared to positive skin tests was calculated by use of the following formula:

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive} + \text{false negative}} \times 100$$

RAST inhibition. RAST-inhibition studies were performed with serum that exhibited the highest IgE binding to CP according to a method previously described.¹² Equal volumes of undiluted test serum were preincubated at 37° C for 2 hours with successive tenfold dilutions of PMSF-inactivated enzyme reagents and then centrifuged at 1500 × g for 15 minutes. The supernatant was removed and incubated with CP-coated methylcellulose discs followed by the addition of ¹²⁵I-anti-IgE. The percent of RAST inhibition was calculated as follows:

$$1 - \left[\frac{\text{cpm } ^{125}\text{I-labeled anti-IgE bound by preabsorbed sample}}{\text{cpm } ^{125}\text{I-labeled anti-IgE bound by nonabsorbed sample}} \right] \times 100$$

RESULTS

Prescreening evaluation

Eighty-four patients received CP skin testing and RAST before CN. Significant CP-specific IgE binding was not detected in any patient before CN. Three patients exhibited positive prick tests to the 10 mg/ml CP skin test reagents before CN. CN was not recommended for these patients, and they underwent surgical laminectomy. RAST binding levels before CN of the three skin test positive patients were 108, 119, and 336 cpm, respectively ($\bar{X}$ cpm = 188 ± 104), and did not differ from the mean of 20 skin test

negative patients ($\bar{X}$ cpm = 109.7 ± 40). The RAST binding percentage in one of the skin test positive patients was borderline positive (336 cpm or 0.96% bound). RAST results in the other two individuals were well within one standard deviation of the mean of the skin test negative control group.

Clinical follow-up after CN

No systemic anaphylactic reactions to CP were encountered in all 81 patients who were prescreened and received intradiscal therapy; however, eight (10%) nonlife-threatening clinical reactions after CN were attributed to CP. All these patients were treated successfully with antihistamines alone. A descriptive summary of the CP-induced immune reactions is presented in Table II. In each case a CP-specific IgE antibody response was documented within 2 to 6 weeks after CN by cutaneous skin testing or RAST. An immediate reaction was observed in one patient (D. H.) despite negative prescreening studies and was characterized by local ocular angioedema beginning 30 minutes after CP injection and resolving 3 days later. It was determined that this patient had experienced prior ocular exposure to papain by the regular use of a soft contact lens cleansing solution containing papain. The second immediate response occurred in a 43-year-old female patient (B. K.) who developed an erythematous rash minutes after receiving discographic radiocontrast material before the CP injection. The rash resolved after treatment with diphenhydramine but was followed by 1 week of diffuse pruritus. Follow-up skin testing and RAST were positive, indicating that pruritus but not the rash may have resulted from IgE-mediated CP sensitization. Six other patients experienced late onset urticarial and angioedema reactions that began 2 to 14 days after CN and

were transient (lasting 1 to 3 days) in duration. In all but one of the eight CP-induced reactions, sensitization was demonstrated by conversion of negative skin tests before CN to positive skin tests after CN. Significant rises in specific IgE after CN from 0 (before CN) to a mean level of 5.5% binding were observed in seven of the eight reactive patients.

Two additional immediate reactions were observed during CN. In these cases there was no apparent sensitization to CP as demonstrated by negative skin tests and RAST before and after CN. The first patient experienced diffuse pruritus, urticaria, and a transient fall in blood pressure that responded immediately to parenteral epinephrine, diphenhydramine, and corticosteroids. This patient had received radiocontrast material before CP injection. Another patient experienced unexplained hives and pruritus within 1/2 hour after CP injection, and these symptoms persisted for 2 weeks after the procedure. The latter patient did not receive iodinated contrast material before CP because of a known prior reaction, but she did receive pre-operative medications that included diphenhydramine and meperidine.

No adverse reactions after CN that followed oral ingestion or ocular exposure to papain products were reported in patients studied prospectively; however, one such type of reaction in a patient evaluated retrospectively is presented below:

C. G., a 24-year-old man, received a CP treatment with no apparent immediate reaction. Four days after CN and within 2 hours after ingesting pork chops prepared with Adolph's meat tenderizer, he noted nausea, diarrhea, and diffuse urticaria. A skin test was positive to papain, and CP-specific RAST binding was 2.9% at that time. This patient has not experienced recurrence of food-induced symptoms after eliminating papaya-derived food products.

Immunologic evaluation after CN

Fifty-two of 81 (64%) patients returned for follow-up skin testing after CN. Of these patients, 19 (37%) developed cutaneous reactivity to CP after CN. Seven of these 19 patients (37%) had experienced immediate and/or late clinical allergic reactions, whereas 12 (63%) did not report adverse responses. Sixteen skin test positive patients after CN were tested to untreated CP as well as boiled and PMSF-inactivated enzyme reagents. Fifteen of these patients exhibited reactivity to untreated CP, and all 16 were reactive to the PMSF-inactivated CP at a concentration of 10 mg/ml. It was noteworthy that none of these 16 patients reacted to the 10 mg/ml of boiled CP reagent, suggesting that the heating process destroyed significant allergenic determinants.

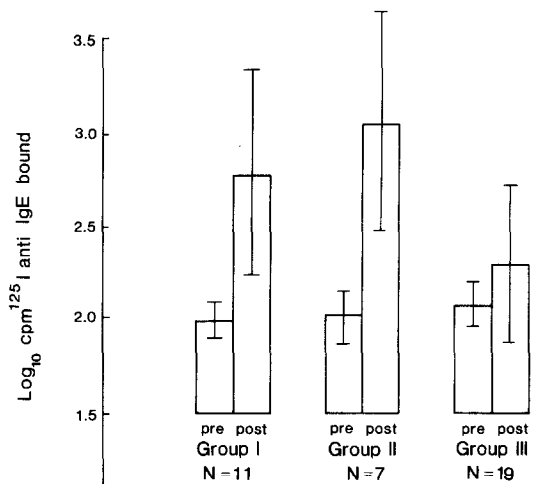


FIG. 1. RAST binding expressed as the means of $\log_{10}$ values of counts per minute ^{125}I -anti-IgE bound before and after CN in patients who developed CP positive skin tests after CN (groups 1 and 2) and in those who remained skin test negative (group 3).

Of the 52 patients who returned for a skin test reevaluation, 38 agreed to have repeat serum RAST determinations. The latter group of patients was divided into three groups: group 1 consisted of 11 patients who were skin test positive after CN in the absence of a reaction, group 2 included seven patients who became skin test positive after CN and had also experienced reactions, group 3 comprised 19 patients who were skin test negative after CN and who had not experienced any adverse reactions, and group 4 consisted of one positive RAST, skin test negative patient who experienced a late clinical reaction after CN. These data are displayed in Fig. 1 that compares before and after mean $\log_{10}$ values in groups 1, 2, and 3. There were no significant differences in these RAST results obtained before CN in the four clinical groups. This is especially noteworthy because the degree of RAST binding before CN failed to predict either subsequent skin test reactivity (groups 1 and 2) or actual clinical reactions (groups 2 and 4). Further analysis of those patients who became skin test positive after CN revealed no difference in RAST binding after CN between group 1 ($\bar{X} = 2.79 \pm 0.54$) and group 2 ($\bar{X} = 3.06 \pm 0.58$); however, mean specific $\log_{10}$ values after CN in the combined skin test positive groups 1 and 2 (2.89 ± 0.57) was significantly greater than in group 3 patients with negative skin tests after CN ($p < 0.002$). The increment of specific binding from before to after CN serum samples was significantly higher ($p < 0.002$) in 18 CP cutaneous reactors in groups 1 and 2 ($\bar{X} = 1672$ cpm) than in

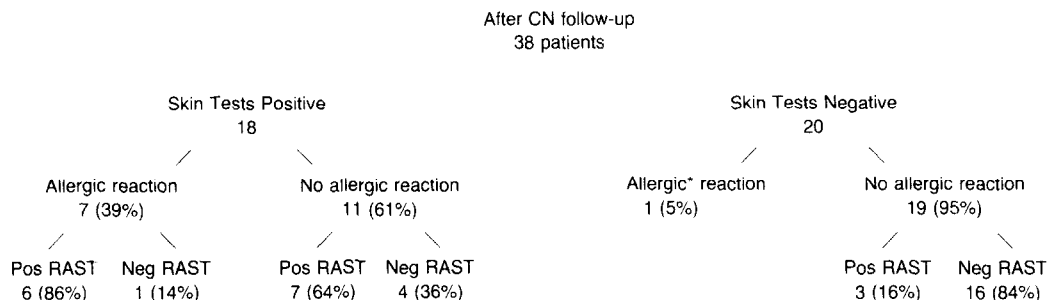


FIG. 2. Summary of RAST and skin test results after CN of 38 patients who returned for follow-up evaluations 2 to 6 weeks after CP injection. *RAST-positive. Pos, positive; neg, negative.

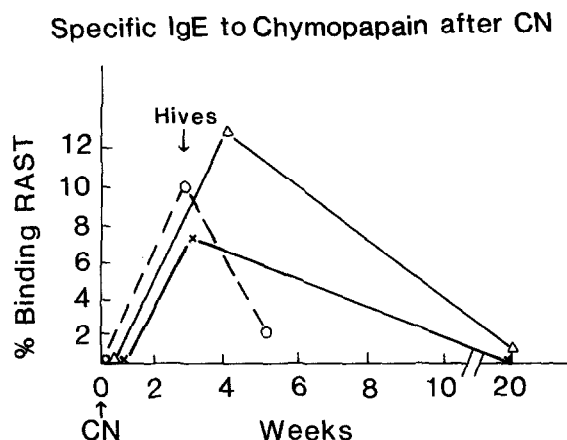


FIG. 3. Serial serum-specific IgE determinations in three patients before and after CN who also acquired cutaneous sensitivity to CP after intradiscal injection. One patient experienced an urticarial response 2 weeks after CN.

19 nonreactors ($\bar{X}$ = 296 cpm) in group 3. Nevertheless, there were three paradoxical instances of skin test negative patients after CN in group 3 with increased CP specific binding of 1.9% (690 cpm), 2.7% (953 cpm), and 9.2% (3248 cpm), respectively.

The immunologic studies after CN in 38 patients are summarized in Fig. 2. The highest prevalence of positive RAST results (higher than 1% binding) was detected in seven of eight patients who experienced clinical reactions (87%). In those patients with positive skin test, 13 of 18 (72%) had positive RAST binding. In contrast, only 3/19 (16%) skin test negative patients without reactions exhibited significant RAST elevations. It should also be noted that 5/18 (28%) patients dermally sensitized after CN would not have been recognized if RAST testing alone was used. In contrast, there was only one RAST positive, skin test negative patient (5%) who became clinically sensitive after CN.

The RAST test was evaluated for sensitivity in iden-

tifying patients developing CP sensitization after CN (groups 1 and 2) by comparison with direct skin testing. The sensitivity of RAST was less than skin testing because only 73% of skin test positive patients were found to have elevated serum-specific IgE. Because seven of eight patients with CP reactions had either positive skin tests or RAST, the sensitivity of either of these methods (87%) was equivalent for identifying the appearance of specific IgE after CN.

Further serial studies in three patients who became skin test positive after CN and concurrently developed elevated levels of CP-specific IgE revealed that antibody responses were transient and fell to baseline levels during varying periods of time. These responses are illustrated in Fig. 3.

RAST-inhibition studies

These studies were performed on undiluted serum of a patient, A. E., who exhibited high CP-specific IgE binding (Fig. 4). Significant inhibition (higher than 50%) of specific IgE against CP was achieved with CP and was also accomplished with the structurally related enzyme, papain. Other serine esterase enzymes (subtilopeptides A and B, esperase, bromelain, trypsin, chymotrypsin, and thermolysin) did not inhibit CP-specific IgE binding. As previously demonstrated in this assay, PMSF pretreatment of papain and CP eliminated the possibility of nonspecific binding of serum proteins to active enzymatic sites without altering significant allergenic determinant domains.

Risk factors

In patients who became sensitized after CN, six of 19 (34%) had positive prescreening prick tests to cat and/or ragweed allergens. A clinical allergic history was elicited from four of these six individuals. In contrast, only two of 19 (10%) nonsensitized patients in group 3 were found to have positive skin tests to the same aeroallergens. There was no significant dif-

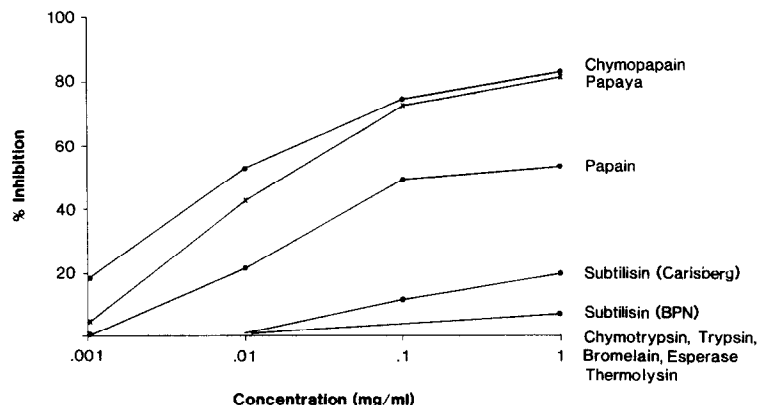


FIG. 4. RAST inhibition studies. Significant inhibition (>50%) of CP-specific IgE binding was demonstrated by papaya, papain, and CP; no inhibition of specific IgE bound to CP was found by other protease enzymatic determinants.

ference between sensitive and nonsensitive patients after CN with regard to prior histories of adverse drug or food reactions.

Two of five patients (40%) who had used papain for cleansing their soft contact lenses became sensitized to CP after CN; however, this did not differ from the overall sensitization rate of 37% in the total study group.

DISCUSSION

CN is an effective procedure for the treatment of patients with lumbar disc diseases¹; however, CP-induced anaphylaxis occurring in 1% of patients has raised questions regarding its overall safety.¹³ This prospective study was planned to evaluate the safety and efficacy of various immunologic methods for detecting presensitization to CP before CN and predicting risk of anaphylaxis after intradiscal injection. The safety of the skin test was demonstrated by the fact that no adverse effects were observed after CP prick testing in patients sensitized to CP both before and after CN.

The relative sensitivity of skin testing and serum-specific IgE for identifying CP-sensitized patients before CN was determined. Eighty-four patients were evaluated before CN. Only three patients (4%) were demonstrated to have IgE-mediated sensitization to CP by skin testing. A significant elevation in serum CP-specific IgE was detected in only one of these patients (33% sensitivity) before CN. Thus, in this study the RAST assay was less reliable than skin testing for identifying patients with specific IgE against CP before CN. If RAST was used as the only pre-screening test before CN, two thirds of the CP-sensitized patients would not have been detected. Al-

though skin test positive patients were not challenged with CP in this study, the validity of a positive skin test for predicting immediate allergic reactions after intradiscal injection was documented by McCullough et al.* In 238 consecutive patients, five of six (83%) individuals with positive skin tests before CN experienced immediate onset allergic reactions after intradiscal CP injection. Thus, based on the McCullough experience, it is probable that the skin test positive, RAST negative patients in this series would have experienced immediate allergic reactions during CN.

The relative sensitivity of CP skin tests and RAST for detecting patients sensitized after CN was also compared. The sensitivity of the skin test for detecting CP sensitization after CN was superior to RAST. However, RAST identified more sensitized patients with positive skin tests after CN (72%) than before the procedure (33%). This difference probably can be attributed to the fact that the quantity of injected CP was large enough to elicit a systemic immune response characterized by a rise in serum-specific IgE. The rise in reaginic antibody was transient and fell rapidly within months after intradiscal injection. In three patients followed on a serial basis after CN, cutaneous reactivity persisted after serum-specific IgE had fallen to baseline levels. Thus, the presence of a serum-specific IgE response after CN appeared to be a function of the quantity of antigen and the time interval since the preceding CP injection.

The serum-specific IgE was also found to rise sig-

*McCulloch J, Canham W, Dolovich J: Skin testing for chymopapain allergy—a preliminary report. (Personal communication)

nificantly after CN in three of 19 patients who did not experience adverse clinical reactions. The latter group did not acquire cutaneous reactivity to CP, suggesting that these specific IgE elevations either were false positive values or that inadequate amounts of IgE antibody were available for sensitization of cutaneous mast cells.

Although no CP-induced IgE-mediated immediate anaphylactic reactions occurred in any of the patients with negative skin tests before CN, immediate local as well as late systemic reactions were observed in 10% of patients during and after the procedure. These reactions have been recognized in the past, but their immunopathogenesis before this study had not been fully explored. These data demonstrated that both immediate and late systemic reactions are mediated by or associated with CP-specific IgE. The development of elevated serum-specific IgE and cutaneous reactivity to CP after CN revealed that systemic sensitization to CP resulted from a single intradiscal injection of the enzyme. It is likely that IgE sensitization was initially elicited by the leakage of enzyme after intradiscal injection and further enhanced by enzyme released 1 to 2 weeks later after discal dissolution. It is possible that late reactions occurring 2 to 14 days after CN may represent accelerated or mild forms of serum sickness associated with formation of IgG antibodies. Immunologic studies are being performed to define further the pathogenesis of these reactions. The immediate onset local ocular angioedema that occurred in one patient (Table II) may have resulted from a preexisting local IgE response to papain contained in his contact lens cleansing agent. Cross-reacting local papain IgE antibodies were not present in sufficient quantities to elicit a severe systemic reaction, as demonstrated by a negative skin test and RAST to CP before CN; however, a rise in specific IgE and the acquisition of cutaneous reactivity to CP after injection with CP suggested that a systemic immune response had occurred. Six other patients who developed late reactions after CN also exhibited conversion of cutaneous reactivity to CP skin test reagents. The mean binding of the clinical reactors (group 2) did not differ significantly from asymptomatic patients with positive skin tests after CN. Thus, the RAST was of no value for discriminating between these two groups.

Interestingly, there were two patients in our group who experienced both immediate and late clinical reactions for which no evidence of IgE sensitization to CP could be demonstrated. The most severe reaction, which was characterized by rash, pruritus, and transient hypotension, may have been in response to a radiocontrast media injection administered before CP.

However, the second reaction could not be explained by a reaction to radiocontrast material because a discogram was not performed before CP injection. Alternative explanations for the above adverse reactions could involve non-IgE mechanisms. These include possible mediator release by an IgG₄ reagin, direct release of preformed vasoactive mediators from mast cells by CP, or direct activation of the complement pathway by CP-immunoglobulin complexes resulting in formation of anaphylatoxins (i.e., C3a, C5a) that subsequently stimulate mast cells. Further studies are necessary to define possible non-IgE-mediated CP-induced adverse reactions.

The positive reference control patient (A. E.) who was not prescreened before CN developed life-threatening anaphylaxis after injection of a test dose of CP despite pretreatment with antihistamines. In contrast to the patients with late systemic reactions who exhibited transient rises in specific IgE against CP, serum-specific IgE remained markedly positive at a 6-month follow-up visit. These data suggest that late reactions may sometimes be associated with transient sensitivity to CP but that CP sensitization associated with anaphylaxis may result in more prolonged serologic reaginic responses. Because of the greater risk of sensitization after CN, repetition of intradiscal CP injection is contraindicated in patients who have exhibited prior cutaneous reactivity to CP.

Atopy, as determined by cutaneous reactivity to selected aeroallergens, appeared to be a significant risk factor for CP sensitization. This finding is in agreement with a previous study that demonstrated an increased risk of allergic respiratory sensitization caused by *B. subtilis* enzymes among atopic detergent workers.¹³

RAST inhibition studies demonstrated cross allergenicity between CP and papain but not between other protease enzymatic determinants. This finding is supported by the observation that a patient sensitized by CP or papain may exhibit cutaneous cross-reactivity to these enzymes. This was observed in the patient who experienced an allergic food reaction to papain in a meat tenderizer 4 days after CN and in whom cutaneous reactivity to both papain and CP were clearly demonstrated. Similarly, in a previous article⁶ we demonstrated cutaneous reactivity to papain as well as CP in an individual with ocular sensitization to papain. Such patients with prior oral or ocular sensitization are probably at high risk for allergic reactions during CN. Conversely, patients with clinical or subclinical sensitization to CP resulting from CN may be at increased risk for subsequent papain-induced allergic reactions. Those individuals sensitized to CP

after CN should be warned about adverse responses to papaya-derived food products and ocular allergic responses to papain in soft contact lens cleansing agents.

Based on this experience, prescreening patients undergoing CN is essential and safe. Skin testing is strongly recommended because it was more sensitive than the RAST for detecting specific IgE against CP both before and after CN. CP-induced sensitization is a common event after CN, and patients should be observed for late clinical reactions within the first month after CN. Although the risk of a severe clinical reaction after a repeat CP intradiscal injection would be expected to be greatly increased, the current study suggests that a subset of skin test negative patients could tolerate a second CP injection; however, a well designed prospective clinical study would be necessary to test this hypothesis.

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