

Incidence and risk factors for latent sensitization to chymopapain: predictive skin-prick tests in 700 candidates for chemonucleolysis

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Summary

Seven hundred patients were investigated prospectively before undergoing chemonucleolysis. A past history of allergy and/or previous exposure to papain, either in food, beverages or drugs, was sought, and a skin-prick test with chymopapain was performed. Based on the results obtained, the subjects were classified into four groups: Group I—225 non-atopic non-papain-exposed subjects; Group II—285 non-atopic papain-exposed subjects; Group III—69 atopic non-papain-exposed subjects; and Group IV—121 atopic papain-exposed subjects. Latent sensitization to papain was observed in 0.4% of subjects in Group I, 3.16% in Group II, 5.8% in Group III and 7.4% in Group IV. The odds ratios were 13.8 for atopy and 7.3 for exposure to papain. Interaction between atopy and papain exposure did not result in a significantly greater risk. Neither sex nor age nor a history of a previous drug reaction were risk factors. Only one patient out of the 23 who were sensitive to papain had no risk factor. The 677 skin-test negative patients then underwent chemonucleolysis and none of them had an anaphylactic reaction. This was significantly less frequent ($P=0.04$) than the incidence in a random population (0.45%). Prick tests performed 6 weeks and 6 months after chemonucleolysis revealed newly acquired sensitization in 36% of the patients. Atopy was not a risk factor for this event. Three points are discussed: (i) the negative predictive value of skin-prick tests with chymopapain is confirmed; (ii) subjects likely to be sensitized are atopic and/or have been exposed previously to food or drugs containing papain and therefore they can be identified pre-operatively by a questionnaire; (iii) atopy is a risk factor for the induction of specific IgE to allergens internalized via a mucosal surface but not for those that are injected parenterally.

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Introduction

Lumbar disc protrusion can be treated by intradiscal injection of purified chymopapain [1,2]. This technique, called chemonucleolysis (CN), carries a risk of anaphylaxis from 0.18 to 0.45% with the first injection [3–6]. A second CN

carries a much greater risk—17% [7,8]. This has led to the recommendation of routine pre-operative skin-prick testing (SPT) with chymopapain [9,10,4]. Latent sensitization to chymopapain, as revealed by skin tests and serological tests for specific IgE antibodies (RAST), has been linked to the ingestion of the papain in papaya [11]. This may explain the relatively high risk for anaphylaxis associated with first CN [2,12]. Nevertheless, a sizeable series of patients is necessary to be certain of this hypothesis. Only one published study [13] meets this requirement.

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Table 1. Food, beverage and drug sources of papain, to be avoided in case of sensitization to papain

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- Contact lens cleaning solutions that contain papain (example: Hydrocar®)
 - Detergent ointments containing papain (example: Pénétradol®)
 - Drugs containing papain: ENT solutions, digestive aids.
 - Chemonucleolysis with Chymodiactine® or Discase®.
 - Papaya in any form; in some cases, also pineapple (source of bromelain); various mixed foods (such as certain appetizer mixes, yogurt, etc.) and beverages that contain exotic fruits.
 - Beer, Coca Cola.
 - Meat tenderizer containing papain.
 - Inhalation of airborne papain and bromelain may occur in industrial settings and in pharmaceutical and biological laboratories. When appropriate, patients should be warned of this possibility.
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In addition, questions concerning the prevalence of latent sensitization to chymopapain and the precise role of the risk factors that have been examined in retrospective [3] and prospective [14] studies have not been fully answered. Hence the need to continue to explore the role of atopy, food allergy and frequent exposure to papain as risk factors for anaphylaxis associated with CN [15,16].

The present prospective study, carried out on 700 patients, confirms the reliability of the negative predictive value of the SPT. Atopy and a history of exposure to papain in food, beverages and drugs are indeed risk factors for allergic sensitization to chymopapain.

Materials and methods

Patients

Between January 1985 and June 1992, 700 out-patients (460 men and 240 women) were entered into this study. Upon inclusion, 24 h before the scheduled CN, each subject was questioned by an allergist about potential risk factors, including atopy and previous exposure to papain. The criteria for a diagnosis of atopy were the following: a history of asthma, atopic dermatitis, allergic rhinoconjunctivitis and/or allergy to any food. A diagnosis of allergic rhinoconjunctivitis or food allergy required a convincing clinical history as well as a positive SPT with the corresponding allergenic extract. The criteria for previous exposure to papain were the following: ingestion at least twice a week of beer, Coca Cola or an exotic fruit, or previous contact with papain in other sources, such as a

contact lens cleaning solution, various digestive aids, Lysopaïne ORL (sublingual tablets containing 2 mg papaya extract plus lysozyme and bacitracin, Boehringer Ingelheim France, Paris, France), etc. (Table 1). For purposes of analysis, the subjects were categorized into four groups:

- I—non-atopic, non-exposed ($n=225$)
- II—non-atopic, papain-exposed ($n=285$)
- III—atopic, non-exposed ($n=69$)
- IV—atopic, papain-exposed ($n=121$)

A SPT with chymopapain was performed. Only those with a negative test then underwent CN. SPT-positive patients were instead instructed to avoid further contact with papain. SPT-negative patients were invited to return for follow-up 6 weeks and 6 months later.

Skin-prick tests

SPT were carried out on the volar surface of the forearm with chymopapain (lyophilized Chymodiactine®) at 2 mg/ml in glycerosaline diluent. The allergenic activity of a solution freshly prepared from lyophilized stock was stable for 15 days, as previously documented [14]. The solution was renewed every 15 days. A negative control with the diluent and a positive control with codeine phosphate were included in each test series. The criteria for a positive SPT, established in advance, were as follows: a chymopapain weal of 2 mm in diameter when the diluent test was negative and the codeine test was only 3 mm, or if the codeine weal was ≥ 4 mm, then the chymopapain weal must be ≥ 3 mm. In the rare cases where the diluent control gave a reaction of 1–2 mm, then the chymopapain test was positive when the diameter of the weal was ≥ 3 mm greater than that of the diluent control (no such cases occurred in this series of patients).

Statistical methods

Comparisons of rates were made with the chi-squared test of conformity and independence, and, when called for, the Fisher test of exact probabilities. Given the size of our patient population and the low frequency of papain-associated events reported in the literature (0.18–0.45%), we used an approximation to a binomial (Poisson) distribution to compare the frequency of the occurrence of these events in our study group with published data. The use of the odds ratio in the search for risk factors was justified by the low frequencies observed. The search for synergy or antagonism between the two major risk factors was carried out with an additive model by multiple linear regression and with a multiplying model by logistic regression [17].

Results

Of the 700 subjects in the four groups, 224 (32%) had no risk factor, 190 (27%) were atopic, (Groups III and IV) and 403 (58%) had a history of exposure to papain (Groups II and IV). In the latter two groups, contact had been as follows: through drinking beer, Coca Cola or exotic fruit juice—27%; through previous treatment with Lysopaine® ORL—19%; through frequent ingestion of exotic fruit—18%; and, most often, through a combination of several of these and other sources of papain—36%.

The SPT was positive in 3.3% of the study population. No patient had a systemic reaction to the test. As shown in Table 2, there were significant differences in the rates of reaction between the groups: in subjects with no risk factor, the rate was 0.44%; in non-atopic papain-exposed subjects, it was 3.16%; in atopic non-exposed subjects, it was 5.8%; and in atopic papain-exposed subjects, it was 7.44%.

The search for risk factors showed that the presence of atopy resulted in a statistically significant odds ratio: 13.8 (1.51–125.5). Exposure to papain resulted in an odds ratio that was not statistically significant, 7.3 (0.92–58.1). Interaction between atopy and exposure to papain did not result in a significant extra risk (threshold at 5%), whether tested with a multiplying model or with an additive model. Thus, interaction did not increase the risk due to atopy or to papain exposure. The odds ratio of the association was, however, statistically significant: 18 (2.25–143.9).

Only one patient (#5) out of 23 with a positive SPT to chymopapain had no risk factor (Table 3). Fourteen of them (60%) were atopic, compared with 25% of the SPT-negative subjects. Nineteen of them (83%) had a history of exposure to papain in food, beverage and/or drugs (Groups II and IV).

One of these patients (#7) had a history of systemic reactions to drugs but denied exposure to papain. Chymopapain sensitivity occurred with equal frequency in males and females (3% vs 3.8%).

Six hundred and seventy-seven subjects subsequently underwent CN without an anaphylactic reaction. In addition to a few patients who developed a rash in the days immediately following the intervention, one case of serum sickness occurred [18]. When the incidence of papain-related events in this group of 677 patients, 0%, is compared with the incidence reported for the general population, 0.45% (based on Bouillet's study [1] of 43 000 subjects), there is a considerable difference ($P=0.04$), assuming that the frequency of the event follows a Poisson distribution [17].

Of the 677 operated patients, 435 underwent an evaluation 6 weeks after CN. At that time, positive chymopapain SPT reactions were significantly more frequent (from 32.3 to 39.7%, depending on the group) than before the procedure, but the difference between any two groups was not statistically significant (Table 2). Only 67 of these patients returned for an evaluation at 6 months; the rate of positive SPT (34%) then was about the same as it had been at 6 weeks.

Thirty-four of the 67 patients had been SPT-positive at 6 weeks, and 21 of them were still SPT-positive at 6 months. The remaining 13 had apparently lost their sensitivity. Of the 33 other subjects (SPT-negative at 6 weeks), two had become sensitive to chymopapain.

Discussion

The aim of CN by intradiscal papain injection is lysis of the proteoglycans of the nucleus pulposus. The risk of anaphylaxis during this procedure is well known and concerns about 0.77% of potential patients [1,4]. The incidence of severe anaphylactic shock is reported to

Table 2. Incidence of positive skin-prick tests to chymopapain before and after chemonucleolysis (CN)

Group	M	F	Total	Before CN		6 weeks after CN		6 months after CN	
				<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
I	143	82	225	1	0.44	42/130	32.3	11/28	39.3
II	191	94	285	9	3.16	69/190	36.3	6/22	27.3
III	44	25	69	4	5.80	16/42	38.1	2/6	
IV	82	39	121	9	7.40	29/73	39.7	4/11	
Total	460	240	700	23	3.30	156/435	35.9	23/67	34.3

I. Non-atopic non-exposed. II. Non-atopic papaine-exposed. III. Atopic non-exposed. IV. Atopic papain-exposed. Two subjects in Group I became SPT-positive between 6 weeks and 6 months after CN.

Table 3. Clinical features of 23 patients who were SPT-positive before chemonucleolysis

Patient no	Sex	Age (years)	Atopy	History of exposure to papain in food (F) and/or drug (D)
1	F	22	+	F
2	F	40	+	D
3	M	33	-	F
4	M	41	-	F
5	F	38	-	—
6	M	24	-	F
7*	F	52	+	—
8	F	36	+	DF
9	F	34	-	DF
10	M	60	+	—
11	M	42	-	DF
12	M	34	+	F
13	M	25	+	F
14	M	30	+	D
15	M	34	+	F
16	M	40	-	F
17	M	32	+	—
18	F	32	+	F
19	M	55	+	F
20	F	53	+	DF
21	M	48	-	DF
22	F	32	-	DF
23	M	34	+	F
Total	14 M, 9 F		14/23	

F. Female. M. Male.

range from 0.18% [13] to 0.45% [7]; it is considerably higher with a second CN [9,12,16]. Eight deaths due to an anaphylactic reaction to chymopapain were reported before 1974 and six more between 1982 and 1986 [5].

Although the medical profession is as yet far from unanimous about CN, many surgeons are convinced of its value [1,4,8,19]. Yet, in a large retrospective study comparing CN and surgical treatment for lumbar disk protrusion, surgery was associated with six times the number of untoward events and 10 times the number of severe accidents [1]. Allergic reactions are probably responsible for half of all known complications of CN [20]. To reduce the risk of anaphylaxis caused by chymopapain a pre-operative prospective evaluation by skin testing has been recommended as it has been shown previously that the risk of anaphylaxis in subjects with a positive SPT or positive RAST is very high [20,21].

The chymopapain SPT has excellent specificity [9,14,20]. When performed by an allergist, the risk of a

false positive test is virtually nil. In addition, its sensitivity is comparable to SPT with other food proteins, better than 80%. One hundred per cent sensitivity is, however, not possible to attain; at least one case of anaphylactic shock during CN has occurred in an SPT-negative patient [22]. The SPT technique now is well standardized and almost without risk. The one reported case of anaphylaxis induced by a chymopapain-prick test may actually have resulted from an intradermal injection of the test solution [23]. RAST is not recommended as an alternative predictive test since it is much less sensitive than the SPT [9].

The negative predictive value of the chymopapain SPT can be estimated accurately only in a very large series of patients. Given that the risk of anaphylaxis is 0.45%, then the number of SPT-negative patients in the present study who underwent CN without incident allows us to say that this test has excellent negative predictive value. This judgement supports the conclusions of Grammer *et al.* [13] and Occelli *et al.* [24], who also observed the total absence of anaphylactic shock in large groups of chymopapain SPT-negative patients.

The prevalence of sensitization to papain in patient populations has been found to be 1.5% [10], 2.4% [24] and, in the present study, 3.3%. The difference between these figures may simply be due to differences between the populations studied. Thus, in screening patients for sensitization to papain, risk factors for sensitization should be taken into account, in particular, previous exposure to papain in foods, drugs and other types of products. Papain is an additive in some brands of beer, and it is present in Coca Cola and beverages containing exotic fruits [25]. It is also used as a meat tenderizer. Papaya itself is present in some packages of mixed foods, such as appetizers. In the present study, the use of a detailed questionnaire revealed very frequent contact with papain, a positive response being obtained in 78% of the subjects.

Since papain is a food protein and atopy is a risk factor for sensitization to other food proteins, it is reasonable to suppose that atopy could be a risk factor for sensitization to papain. In the study of Cornaille *et al.* [10], however, a positive SPT to chymopapain was obtained in 1.7% of the atopic subjects compared with 1.3% of the non-atopic subjects, leading those authors to conclude that atopy is not a risk factor for sensitization to papain. Based on an analysis of 104 cases, Garcia-Ortega reached a similar conclusion [26]. In contrast, the present study of 700 patients revealed a significant difference between the two classes of patients, since the prevalence of a positive SPT in non-exposed atopic subjects was 5.8% compared with only 0.44% in non-exposed non-atopic subjects. Furthermore, previous exposure to papain was also a risk factor, increasing the prevalence of sensitization from 0.44% to

3.16% in our non-atopic subjects. The fact that a positive chymopapain SPT was rare among our non-atopic non-exposed subjects—occurring in only one out of 225 cases—provides additional evidence that both atopy and previous exposure are risk factors for sensitization to this protein. Conversely, drug allergies did not appear to be a risk factor. It should be noted that the mechanism of allergy to common drugs, which are low molecular weight substances, is quite different from that of allergy to proteins [3,16].

According to Garcia-Ortega *et al.* [26], the intradiscal injection of chymopapain results in sensitization in 16% of cases, but according to Bernstein *et al.* [9] in as many as 37%. The latter figure is based on both SPT and on RAST in subjects tested from 2 to 6 weeks after CN. We found a similar incidence of positive SPT at 6 weeks post-CN, and two-thirds of our subjects who were seen at 6 months were still sensitized while only two out of 33 subjects who were negative at 6 weeks became SPT-positive at 6 months. It is interesting to note that the incidence of sensitization after intradiscal injection did not differ between groups. In particular, atopy did not predispose patients to a higher risk of sensitization to chymopapain in those who were not sensitized before CN. Likewise, atopy does not appear to be a risk factor for allergy to hymenoptera venom. These interesting data support the hypothesis that atopy cannot be considered as merely an abnormal IgE antibody response to environmental proteins [11]. The present study shows that, although atopy did not influence the response when chymopapain was injected, when this antigen entered the body across a mucosal—for the most part, digestive—surface, then atopic individuals were likely to produce specific IgE. It is certain that the antigenic information transmitted by antigen presenting cells in the intestinal mucosa is critical for the IgE response to this environmental protein. One might therefore postulate that in atopic individuals there is an immunological anomaly in mucosal antigen presenting cells, and that this anomaly might concern the antigenic information they transmit.

Hall and McCulloch recognized the clinical risk of allergy to papain following CN [2,3]: two out of 15 of their secondarily sensitized patients suffered an allergic reaction after ingestion of papain in food or in a drug. For this reason, it is ethically imperative to advise any patient who has a positive SPT to chymopapain to avoid foods, beverages and drugs containing papain (see Table 1). This advice was given to our patients and none of them has subsequently experienced an allergic reaction that could have been due to papain. Thus, this simple recommendation appears to be effective.

The most important problem that remains is the current uncertainty of the real risk of an allergic reaction

during CN in patients who are sensitized to chymopapain. In order to avoid a reaction in 0.45% of patients, one would advise against CN in the 3.3% of patients who are SPT-positive, eight times more than the number actually at risk for one. One should also consider the rate of sensitization after a single CN (33%) with the incidence of allergic reactions that accompanies a second CN (17%, when a predictive SPT has not been done). Insofar as the SPT is simple to do, the present study as well as those previously published favour its use to predict sensitivity to chymopapain.

Conclusion

There should be no question about the ethical justification of predictive skin testing with chymopapain since the detection of sensitization dictates the need to avoid this potentially lethal substance. The observation that no anaphylactic reaction occurred in the 677 patients with a negative chymopapain SPT who underwent CN underlines the excellent negative predictive value of this test. The problem of which patients to test remains debatable [27]. Some authors deny that there are identifiable risk factors and recommend doing predictive SPT and a RAST in every patient undergoing CN [9,26]. The present study demonstrates that predictive skin testing with chymopapain could be reserved for patients at risk, and that such patients could be identified with a simple questionnaire that focuses on atopy and frequent exposure to papain. Indeed, at least 96% of pre-operatively sensitized patients can be identified by this means. On the other hand, the high rate of sensitization after a first CN and the high incidence of anaphylactic reactions associated with a second CN mean that an SPT with chymopapain should be mandatory before a second CN.

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