TEST EVALUATION
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TEST

Chymopapain Sensitivity Test (Serum)

METHOD

Modified radioallergosorbent assay

CLINICAL APPLICATIONS

Chymopapain chemonucleolysis has become a viable option in the treatment of lumbar discs failing to respond to conservative therapy. The efficacy has been demonstrated in recent double-blind studies (1,2). Although relatively safe, occasional patients will exhibit an anaphylactic shock-like reaction upon injection of chymopapain. The reported incidence of anaphylaxis ranges from 0.18% to 1.0% (3,4). This rate may be further reduced by appropriate precautions and pretreatment medication (5).

A laboratory test has been developed to measure serum levels of immunoglobulin-E (IgE) directed against chymopapain. This test has been recommended by some as a pre-treatment screen for all patients considered for chemonucleolysis to preclude anaphylaxis. Data on test performance have not been published in an edited journal. A brochure has been distributed describing a preliminary study of 763 patients screened for chymopapain sensitivity (6). Some patients underwent subsequent chemonucleolysis and complications were recorded.

CLINICAL AND TECHNICAL LIMITATION

Patients with negative test results experienced anaphylaxis at a rate similar to unscreened populations (Table I). Of 517 patients placed in a "below borderline range" (IgE < 0.03 IU/ml), anaphylactic reactions occurred in 0.77%. This does not differ appreciably from the incidence of anaphylaxis in large unscreened populations previously reported.

The data were apparently derived from a population with a greater prevalence of anaphylactic responders than has been previously described. The high trait prevalence in the experimental population causes the predictive value of a positive test to be increased. In contrast to the low rate of anaphylaxis in published studies (0.18–1.0%), subjects showed a 2.0% incidence of anaphylaxis. The data further predict that 66.7% of "high risk" patients would exhibit anaphylaxis upon chymopapain injection. Had all "high risk" patients undergone chemonucleolysis (most were deferred) an additional 43 anaphylactic episodes might have occurred, raising the prevalence of anaphylactic responders to 6.6%. If the prevalence of anaphylactic sensitivity in the clinical population is less, as there is reason to believe, then a large proportion of positive test results become false positives.
Although the patients were tested prospectively, the study was not double-blind. This is evidenced by the large number of treatment deferrals in the "high risk" groups. The lack of a double blind format may be significant because the study endpoint was not well defined. Surgeons, informed prior to chemonucleolysis that their patient was at increased risk, might be quick to intervene at the first sign of allergic reaction. They might thus classify a mild reaction as severe anaphylaxis. This pre-treatment bias effect is suggested by the finding that 11 of 15 patients with any allergic response had severe anaphylaxis. This is in contrast to the Watts study which showed only a fraction of total allergic reactions (12%) will approach the severity of anaphylactic shock.

If a positive result is considered an IgE level greater than or equal to 0.06 IU/ml, calculations based on treated patients show a test sensitivity of 36% (approximately 1/3 of anaphylactic responders would be detected). The test specificity (percent of normal patients with negative results) is difficult to judge due to the large number of treatment deferrals. A value of 99% is assumed. If the prevalence of anaphylactic responders were 0.25%, then for 1000 consecutive patients screened, 1 case of anaphylaxis would be averted, 2 cases would be missed, and 10 patients would be inappropriately denied chymopapain therapy. The cost of screening would be $60,000.00 at the current test charge. Additional cost and risk would accrue to the 10 patients sent directly to more invasive type therapy (surgery).

A second commercially available chymopapain allergy test has a sensitivity of 57% and a specificity of 97% (7). This test would miss approximately 1/2 of anaphylactic responders and inappropriately exclude 30 patients from chemonucleolysis, assuming the above trait prevalence (0.25%) for 1000 consecutive patients screened.

The current data do not establish the usefulness of chymopapain sensitivity testing as a general pre-operative screening test. A careful cost-benefit analysis, based on precise test sensitivity, specificity and trait prevalence, should be performed. Chymopapain sensitivity testing may prove to be useful in a select group of patients in certain clinical circumstances. The role of chymopapain sensitivity screening in the general clinical population, prior to chemonucleolysis, remains to be conclusively demonstrated.

REFERENCES


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Table I. *Allergic Reactions According to Chymopapain-specific IgE Levels

<table>
<thead>
<tr>
<th>Chymopapain-specific IgE, serum (IU/ml)</th>
<th>0.00-0.01</th>
<th>0.02-0.03</th>
<th>0.04-0.05</th>
<th>0.06-greater</th>
<th>TOTAL PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients screened</td>
<td>541</td>
<td>115</td>
<td>43</td>
<td>64</td>
<td>763</td>
</tr>
<tr>
<td>Chemonucleolysis performed subsequent to screening</td>
<td>425</td>
<td>92</td>
<td>34</td>
<td>6</td>
<td>557</td>
</tr>
<tr>
<td>Total allergic reactions, including questionable/mild reactions</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Severe/anaphylactic reactions</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

*Data on file, Allergenetics Reference Laboratory, 8/16/83.
Clinical Summary

This was the sixth hospital admission of this 78 year old man who was transferred from another hospital where he was diagnosed to have a right middle lobe pneumonia, congestive heart failure, and digitoxic rhythm. Present illness dates back many years, includes hypertension controlled with Minipress, hydrochlorothiazide and Anturane. The patient was in his usual state of health until May, 1984 when he was found to have a hemoglobin of 10.5 grams with occasional hypersegmented PMNs. The B-12 level was low and the patient was presumed to have pernicious anemia. The patient developed an urticarial rash after two B-12 injections. He was treated with Benadryl and prednisone which resulted in mild mental deterioration. The patient was admitted to Rehabilitation Service on 8/13/84 and CT scan showed possible old ischemic infarction in the right frontal area. The patient was last admitted to Mount Zion on 10/8/84 with marked confusion and weakness. He was treated with Lasix for congestive heart failure. On 11/21/84 the patient was found to have multifocal atrial tachycardia with a rate of 140 and a blood pressure of 140/80. The patient was put on Digoxin at this time. On 11/29/84 the patient awoke in the middle of the night with profound shortness of breath and was admitted in San Francisco General Hospital. At the time of admission his white count was 16,900 with a hemoglobin of 13.9 grams. Blood gas revealed a pH of 7.37, PCO$_2$ of 41.6, and PO$_2$ of 72 with 100% oxygen. The patient was intubated. Chest X-ray showed a right middle lobe infiltrate. CPKs give no evidence of myocardial infarction. On physical exam the patient's blood pressure is 170/80, an irregularly irregular rhythm with systolic murmur. Chest auscultation also showed bilateral pulmonary rhonchi. A sputum culture grew Staphylococcus aureus and the patient was started on Sulfoxaphane. The patient had a series of CK isoenzymes. The total rose from 65 on November 29, 1984 to 372 on December 1, 1984. An unusual finding was the patient persistently had 50 to 60% CK1 and only up to 4% CK2. EKG showed some ST depression and it was thought that the patient had a myocardial infarction. The patient's pneumonia did not improve by chest X-ray. The white blood cell count increased to 19,000 and the patient was switched to Vancomycin. The urine output was decreased and the patient was given IV Lasix. The patient continued to go downhill and died on 12/8/84.

At autopsy the patient had a 5 cm grey-white firm tumor in the right middle lobe, apparently originating from the main bronchus. There was gross metastatic tumor to hilar and mediastinal lymph nodes. The liver was extensively infiltrated by tumor modules ranging from 2-3 cm in size. Microscopic sections of vertebral column bone also revealed involvement. No acute myocardial infarction was seen. The brain was grossly and microscopically unremarkable.
Methods

A cell suspension was prepared from a 3x3x2 cm piece of the lung tumor by grinding the tissue with a mortar and pestle with 10 ml of saline. The suspension was centrifuged at 1500 g, and the supernatant extracted. The total CK value measured 420 U/L (Beckman ASTRA). Electrophoresis (Corning aca) revealed 81% CK3 (MM), 19% CK1 (BB), and no CK2 (MB).

Discussion

Creatine kinase is a tissue enzyme catalyzing the reaction:

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\text{creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{creatine} + \text{ATP}
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There are 3 dimeric enzymes composed of the 2 subunits: the so-called M (muscle) and B (brain). CK3 (MM) is the predominant form found in muscle (skeletal and cardiac). CK2 (MB) is present in relatively high amounts in cardiac muscle. Its presence in serum is classically used to diagnose myocardial infarction. CK1 (BB) is normally found in CNS tissues, smooth muscle (especially uterus and small bowel), prostate, and kidney. CK1 of CNS origin is not normally seen in the systemic circulation unless the blood brain barrier has broken down.

High levels of circulating CK1 as a tumor marker for lung carcinoma were first reported in 1975 by Coolen & Pragay (1). A second study in 1978 (2) showed CK1 in the peripheral circulation of 1 of 5 patients with lung carcinoma. In a more extensive study by Coolen et al. (3), 39 patients with lung cancer were examined. Twelve of 15 patients with small cell carcinoma and 1 of 3 with adenocarcinoma showed CK1 actively. Another study by Griffiths found 54% of patients (35 of 65) with small cell carcinoma, 27% (5 of 16) with squamous carcinoma, and 12% (3 of 24) with adenocarcinoma of the lung to have CK1 activity in the serum.

A case was described by Goffman et al. where up to 69% CK1 activity in the serum was noted in a patient with mixed small and large cell carcinoma. Although electrophoresis showed 10% CK2, no evidence of myocardial infarction was seen at autopsy (5). These findings parallel ours very closely. An interesting study by Gazdar et al. of 67 patients with small cell pulmonary carcinoma showed normal CK1 when disease was limited, but 16 of 41 with extensive disease had elevated levels of CK1 (6).

The fact that neither we nor Goffmak et al. (5) found evidence of myocardial infarction despite the presence of 4% and 7% of CK2, respectively, is somewhat surprising. A possible explanation may be the misinterpretation of CK1 as CK2. There is a well described phenomena in which IgG complexes with CK1 may then migrate in the area usually interpreted as CK2. The fact that RIA of our patient sample failed to reveal significant amounts of CK2 lends some support to this hypothesis.

CK1 does not appear to be a sensitive or specific tumor marker for pulmonary neoplasia. However, when unexpectedly high levels of CK1 do appear, lung carcinoma, particularly small cell, should be considered.
References


