Comparison of the Skin Test and ImmunoCAP System in the Evaluation of Mold Allergy

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Background: Mold is ubiquitous in our environment and is a common allergen in allergic diseases. The skin test and the Pharmacia ImmunoCAP system (CAP) for assay-specific immunoglobulin E (IgE) antibodies are both widely used. The goal of this study was to compare the performance of the skin test and CAP in the evaluation of mold allergy.
Methods: Patients with allergic rhinitis were enrolled at our outpatient department. The diagnosis of allergic rhinitis was based on typical symptoms for more than 2 years. All patients were tested by both intradermal skin test and serum assay for specific IgE antibodies. The skin test included house dust, cotton, ragweed, and 5 fungal antigens (*Candida*, *Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*). The serum-specific IgE antibodies were quantified using the radioimmunoassay version of CAP.
Results: Seventy-five patients (44 males and 31 females) with allergic rhinitis were enrolled in this study. Their ages ranged from 12 to 76 years old, with a mean of 31.9 years. The positive rates of skin test and CAP were 56.0% versus 9.3% for *Candida*, 22.7% versus 1.3% for *Alternaria*, 16% versus 9.3% for *Aspergillus*, 14.7% versus 1.3% for *Cladosporium*, and 32% versus 8% for *Penicillium*. There were statistically significant differences between the positive rates for *Candida*, *Alternaria*, *Cladosporium*, and *Penicillium* when analyzed by the McNemar test.
Conclusion: The positive rate of the skin test is higher than CAP when evaluating mold allergy. Clinicians should note that a discrepancy may exist between the results of *in vitro* and *in vivo* tests when evaluating mold allergy. [*J Chin Med Assoc* 2006;69(1):3–6]

Key Words: allergen, fungi, intradermal tests, rhinitis

Introduction

Mold is ubiquitous in our environment and is a common allergen in allergic diseases.[1–5] There are 2 major approaches in allergen tests: the skin test (*in vivo*) and serum assays for allergen-specific immunoglobulin E (IgE) antibodies (*in vitro*). *In vitro* tests have traditionally been considered less sensitive than skin tests for investigation of mold allergy.[6–10] This has been attributed to technical problems such as difficulty in binding the mold antigen to the carrier substrate. The Pharmacia ImmunoCAP system (CAP) is a second-generation *in vitro* test using a 3-dimensional cellulose solid allergen phase. Some studies reported that CAP had diagnostic performance similar to that of the skin test.[11–15] Our previous study found CAP achieved sensitivity similar to that of the skin test in detecting allergy to house dust, but the positive rates of CAP were significantly lower than those of the skin test when diagnosing allergy to pollen, dog dander, and *Candida*.[10] Only a few studies have reported on the performance of CAP in the evaluation of mold allergy.[9–12] The purpose of this study was to compare the performance of the skin test and CAP in the evaluation of mold allergy.

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Methods

This study was undertaken after approval by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan, R.O.C. From September 2003 to February 2004, patients with allergic rhinitis were enrolled from the ENT outpatient clinic in Taichung Veterans General Hospital. The diagnosis of allergic rhinitis was based on the clinical criteria gold standard: typical clinical history and apparent symptoms of sneezing, rhinorrhea, nasal itching, and/or nasal obstruction for more than 2 years.[15] Patients who had taken any antihistamine within 1 week or astemizole within 3 months were excluded.[16,17] Patient evaluation included serum CAP test (Pharmacia, Uppsala, Sweden) and intradermal skin test (Tori Ltd, Tokyo, Japan). The skin test included house dust, cotton, ragweed, and the 5 fungal allergens (*Candida*, *Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*). The volar surface of the forearm was used for intradermal testing. About 0.02 mL of each extract alone with control solutions (histamine for positive control and normal saline for negative control) were intradermally injected; the size of wheal was 4 mm in diameter. The skin reaction was read 15–20 minutes after the injection. If the wheal diameter was more than 9 mm or the diameter of erythema was more than 20 mm, the reaction was considered positive. The IgE antibodies to these 5 fungal allergens were measured with CAP and regarded as positive if the values were ≥ 0.35 kU/L. The results were analyzed by the McNemar test.

Results

A total of 75 patients (44 males and 31 females) were enrolled in this study. Their ages ranged from 12 to 76 years old, with a mean age of 31.9 years. Sixty-eight patients (90.6%) had positive skin test results. Fifty-five patients (73.3%) had positive skin reactions to fungal allergens. The positive rates of the skin test and CAP were 56.0% versus 9.3% for *Candida*, 22.7% versus 1.3% for *Alternaria*, 16% versus 9.3% for *Aspergillus*, 14.7% versus 1.3% for *Cladosporium*, and 32% versus 8% for *Penicillium* (Table 1). The results were compared using the McNemar test and showed statistically significant differences in the positive rate of the 2 testing methods in *Candida*, *Alternaria*, *Cladosporium*, and *Penicillium* (p = 0.000, 0.000, 0.006, and 0.001, respectively).

Table 1. The results of the skin test and CAP test

	Skin test +	Skin test –
Candida		
CAP +	7	0
CAP –	35	33
Alternaria		
CAP +	1	0
CAP –	16	58
Aspergillus		
CAP +	2	5
CAP –	10	58
Cladosporium		
CAP +	0	1
CAP –	11	63
Penicillium		
CAP +	2	4
CAP –	22	47

Discussion

Detection of allergens and allergen avoidance are crucial in the treatment of allergic diseases. The skin test (*in vivo*) and serum assay for specific IgE antibodies (*in vitro*) are currently the 2 general approaches in wide use. Both have their own advantages and disadvantages. The skin test is more sensitive but is uncomfortable and time consuming. The skin reactions can be influenced by certain medications and dermatologic conditions.[15–17] The *in vitro* test is less sensitive, but medications or skin conditions will not influence results. Thus, the *in vitro* tests are more specific.

A number of different *in vitro* methods have been devised. CAP is a clear advance in *in vitro* testing because of its unique solid phase and antibody system.[11–16] Some studies have reported the performance of CAP to be similar to that of the skin test.[11–15] But the sensitivity of CAP can vary between different inhalant allergens.[10,14] A study performed by the senior author (R.S.J.) found CAP achieved sensitivity similar to that of the skin test (Tori Ltd) in detecting dust allergy. However, the positive rates were significantly lower than those of the skin test in detecting pollen, dog dander, and *Candida*.[10]

The identification of mold allergens is problematic. The clinical history is rarely conclusive for mold allergy, since seasonal variation may coincide with variations in pollen and mite allergens. Currently, up to 80,000

species of fungi have been described. They are also known to mutate frequently; therefore, an extraordinarily large number of variants exist. The fungal antigens have more complex macromolecular composition than other allergen sources. The characterization, purification, and standardization of allergens from such a wide range of fungal species are very difficult.[18–22] Many commercial allergen extracts show variable potency.[21–23] Also, the coupling of the allergen extract to the insoluble solid phase of the *in vitro* test is limited because of the complex composition. It is traditionally thought that the *in vitro* tests are less sensitive in the evaluation of mold allergy than the skin test.[6–10] In our results, the positive rate of the skin test was higher than that of CAP. There were significantly different positive rates between the 2 testing methods among 4 of 5 fungi.

Another possible reason for the discrepancy between the results of the skin and *in vitro* tests is the use of different allergens in the 2 tests.[6,18] There are subtle differences in antigens used in the skin test and CAP: *Alternaria kikuchiana* versus *Alternaria tenuis*, *Cladosporium cladosporioides* versus *Cladosporium herbarum*, and *Penicillium luteum* versus *Penicillium notatum*. Different species in the same genera could have allergenic differences.[24–27] To the best of our knowledge, there are no reports about the degree of cross-reactivity between these 3 different pairs of mold allergens. Because a huge number of variant strains exist, the selected allergen of commercially available extracts for the skin test could be different from the allergen of the *in vitro* test. Different strains could have different allergenic properties, and result in different positive rates. We found similar situations in previous studies comparing skin tests and *in vitro* tests.[6,28]

Neither the *in vivo* nor the *in vitro* approach provides an ideal solution. The results of allergy tests should be interpreted in conjunction with clinical history and physical findings. Optimal use of allergy tests requires a high level of knowledge regarding allergen composition, distribution, local importance, and selection of adequate test method. Furthermore, it is important to point out that all methods have both advantages and disadvantages.

The diagnosis of mold allergy is based on clinical history and the evidence of IgE-mediated sensitization to mold. Since the clinical history is rarely conclusive for mold allergy, an allergy test mainly determines the diagnosis of mold allergy. Our results showed that the positive rate of the skin test was significantly higher than that of CAP in detecting mold allergy. King[29] has suggested that the skin test, with its higher sensitivity, could be used as the primary screening test and CAP, with its higher specificity, could be a confirmatory test.

In conclusion, the skin test and CAP are 2 major approaches for detecting allergens. Our results showed the positive rate of the skin test was higher than that of CAP in the evaluation of mold allergy. Clinicians should note that a discrepancy may exist between the results of *in vitro* and *in vivo* tests when evaluating mold allergy.

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