A Study of Clinical Correlations between Skin Test, Radioallergosorbent Test and Bronchial Provocation Test in House Dust Asthmatics

Chein Soo Hong, Ki Baik Hahm, Seung Heon Oh, Hae Sim Park, Kap Bum Huh and Kihoo Kim

We evaluated the correlations between the allergy skin test for house dust, radioallergosorbent test (RAST) and the bronchial provocation test for revealing the sensitivity of the skin test and RAST, and for aiding in the search for the causative allergen in house dust asthmatics. There was an overall 72.5% agreement between the prick test and RAST, a 73.8% agreement between the prick test and house dust bronchoprovocation test (HD-BPT), and a 71.3% agreement between HD-BPT and RAST. A positive RAST was found with a positive HD-BPT in 71.2% of cases, and if RAST was negative, HD-BPT was negative in 46.9% of cases. 69.6% of the positive cases on prick test (more than 21 mm of erythema) were positive with RAST. All of the cases with a negative skin reaction to the prick test were negative to RAST. A positive skin test was found with a positive HD-BPT in 77.1% of cases, and if the prick test was negative, the HD-BPT was negative in 50.0% of cases. 87.5% of cases with a RAST positive exhibited a positive result with HD-BPT. A significant correlation was found between the results of prick tests and those of RASTs in the early response group of HD-BPT, but not in the late and dual response groups. There were significant correlations between total serum IgE and the results of HD-BPT, and total serum IgE value and the results of RAST. The greater the size of the prick test, the greater the likelihood of a positive HD-BPT. All 5 cases with an end point of intradermal skin test of a 5^−5^×10^−2^ dilution of house dust noted a negative HD-BPT. There was no significant correlation between total serum IgE and total eosinophil count. There was no significant correlation between wheal and erythema size of prick test and PC_20 of methacholine.

Key Words: Allergy skin test, bronchial inhalation challenge test, radioallergosorbent test, methacholine bronchial provocation test. house dust allergen.

Several different laboratory tests have been proposed to screen for respiratory allergens and to search for the causative allergen, which might be the most important one in allergic disease.

Since Kern (1921) discussed the importance of house dust in respiratory allergy, skin tests remain useful in finding the relationship between the offending allergen and bronchial asthma because of its ease of performance, high degree of reproducibility, and good correlation with in vitro measurement of specific IgE. However, the results of skin tests are variable according to the condition of the patients, testing allergens and many other factors (Imber 1977).

After demonstration by Ishizaka and Ishizaka (1966) that skin sensitizing antibodies belong to the IgE class of immunoglobulins, many studies have demonstrated a correlation between skin reactivity, serum IgE and challenge tests (Loeffler et al. 1973).

According to Townley et al. (1975, 1979), methacholine sensitivity of the bronchial tree has become a valuable and widely used technique for studying the irritability of the airways. He confirmed that the diagnosis of asthma could be possible during symptom free periods by the methacholine bronchial challenge test.

This study was undertaken to evaluate the correlations between the allergy skin test, the radioallergosorbent test, and the bronchial challenge test in house dust asthmatics, and to examine the sensitivity and specificity of the skin test and RAST and their usefulness in the search for offending the allergen in bronchial asthma.
MATERIALS AND METHODS

Subjects

The present study includes 80 adult asthmatic patients, who showed positive reactions to the routine house dust skin test and were subjected to allergological investigations in the Department of Internal Medicine, Yonsei University College of Medicine. Patients consisted of 34 male and 46 female patients, ranging in age from 14 to 65 years (Table 1).

All of the patients discontinued medications prior to testing as follows: no bronchodilators for six to 12 hours, no antihistamines for 48 hours, and no cromolyn sodium for 48 hours (Chai et al. 1975). Also, they had no immunotherapy previously.

Methods

The patients’ allergy histories carefully evaluated, and their total peripheral eosinophil counts and total serum IgE (PRIST) were determined.

The prick skin test with house dust allergens from the Bencard Co. (England) was carried out on the backs of all subjects. The results were interpreted 15 minutes later according to the measurement of the mean diameter of wheal and erythema, and rated from negative to four plus. Intradermal skin tests were done at the lateral aspect of the arm using a serial fivefold dilution of house dust allergen (Tori Co., Japan, for immunotherapy 1:10 w/v) starting from a 1:100 dilution with 0.4% phenol 0.9% saline. The reaction was regarded as positive when the mean diameter of the wheal was 7 mm 15 minutes after the intradermal injection of 0.01 ml.

Methacholine bronchial provocation test (M-BPT) was performed with the 5000 II Pulmo Lab system according to the standardization of bronchial inhalation challenge test by Chai et al. (1975). Forced expiratory maneuvers from vital capacity (VC) to residual volume (RV) were taught to the subjects, and maximal expiratory flow volume (MEFV) curves were obtained. The tests were repeated until the subjects were accustomed to the test. The resulting data, such as forced expiratory volume for one second (FEV), forced vital capacity (FVC), and maximal midexpiratory flow rate (MMER) were considered as a baseline. Saline was inspired 5 times from residual volume to vital capacity using a vaporephrine nebulizer with 20 psi compressed air. Three minutes later the pulmonary function test was repeated by the same methods as baseline and considered as a comparable baseline. With saline inhalation, if there was not a specific change of FEV, (less than 15% from baseline), M-BPT was performed subsequently. Three minutes after five inhalations of each diluted methacholine solution (0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5.0, 10, 25 mg/ml), the pulmonary function test was reevaluated. The changes in pulmonary function during M-BPT were compared with the comparable baseline data and expressed as percent of changes. If the percent decline of FEV, is more than 20%, M-BPT is considered to be a positive test. The inhaled methacholine concentration at the positive response is designated as the bronchial threshold of methacholine. PC20 of methacholine is the concentration of methacholine in which FEV, is decreased at 20% of comparable baseline.

House dust bronchial provocation test (HD-BPT) was performed by the same method as in M-BPT, using house dust allergen (Tori Co., Japan, for immunotherapy 1:10 w/v). The usual starting concentration of allergen for HD-BPT was 1:500 w/v, diluted with 0.4% phenol-0.9% saline. House dust extracts were inspired 5 times on vital capacity through a vaporephrine nebulizer. Pulmonary function was reevaluated ten minutes after the inhalations. If there was not a significant of FEV, (less than 15%), the next higher concentration 1:100 dilution was inhaled. In this manner 1:50 and nondiluted (1:10 w/v) solutions were challenged until more than a 20% reduction of FEV, was obtained. If no reduction occurred the nondiluted solution of house dust was challenged once more. The final step was two challenges of undiluted solution of Dermatophagoides farinae for immunotherapy (Tori Co., Japan, 1:1000 w/v). Pulmonary function tests were measured every 10 minutes for the first 60 minutes in order to observe early bronchoconstriction response, and every hour for eight hours to observe late or dual bronchoconstriction response (Pepys and Hutchcroft, 1975).

Radioallergosorbent test (RAST) for house dust (Bencard, h4) and Dermatophagoides farinae (d4) was measured by using the RAST kit (Phadebas Co.), which

Table 1. Age and sex distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–20</td>
<td>8</td>
<td>3</td>
<td>11 (13.8)</td>
</tr>
<tr>
<td>21–30</td>
<td>8</td>
<td>24</td>
<td>32 (40.0)</td>
</tr>
<tr>
<td>31–40</td>
<td>8</td>
<td>14</td>
<td>22 (27.5)</td>
</tr>
<tr>
<td>41–50</td>
<td>5</td>
<td>5</td>
<td>10 (12.5)</td>
</tr>
<tr>
<td>51–60</td>
<td>4</td>
<td>0</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>61–65</td>
<td>1</td>
<td>0</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Total: 34 46 80 (100.0)

Male: Female = 1:1.35
used radioimmunoassay methods designed by Johansson et al. (1967). The results were interpreted according to the reference sera from zero to class four. We classified as a group of RAST positive if any one or both of two allergens (h3, d3) revealed class 1-4 in RAST.

**RESULTS**

**Comparison of the results of skin tests to those of HD-BPT**

A positive skin test (more than 21 mm of erythema on prick test) was found with a positive HD-BPT in 54 of 70 cases (77.1%), however when the skin test was negative (less than 21 mm of erythema on prick test), the HD-BPT was positive in 5 of 10 cases (50%). Overall, there was 73.8% agreement between these two tests (Table 2).

The greater the size of the prick test, the greater the likelihood of a positive HD-BPT. One of three cases (33.3%) with a negative skin reaction on prick test noted positive HD-BPT. Thirty-three out of 39 cases (84.6%) with a 4+ skin reaction to the prick test showed a positive HD-BPT. But, statistically there was no relationship between the reaction criteria of the prick test and positivity of HD-BPT (r=0.28) (Table 3).

With regard to the intradermal skin test, in more diluted solutions produced a positive reaction, the chance for a subsequent positive HD-BPT was greater. There were no positive BPT in 5 cases with the end point skin reaction at 5°-5×10⁻² dilution of house dust. One third of the cases with an end point reaction to 5°-5×10⁻² dilution showed positive HD-BPT. Thirty-five out of 39 cases (89.7%) which exhibited an end point skin reaction at dilutions greater than the 5°×10⁻², noted positive HD-BPT (Table 3). There was good correlation between the end point of the intradermal skin test and the positivity of HD-BPT (r=0.65).
Results of HD-BPT according to bronchial threshold of M-BPT

More positive rates of HD-BPT were found in groups of subjects having a low or moderate methacholine threshold (85.7% and 81.1%), as compared to that of the high methacholine threshold group (58.6%, Table 4).

Comparison of the results of RAST to HD-BPT

When RAST was positive (class 1 to 4), a positive HD-BPT was found in 42 out of 48 cases (87.5%), but a negative RAST was found in 17 of 32 cases (53.1%) with a positive HD-BPT. Overall, there was a 71.3% agreement between these two tests. The sensitivity of RAST to HD-BPT was 87.5% and the specificity of RAST to HD-BPT was 46.9%. A positive predictive value of RAST to HD-BPT was 71.2%, and a negative predictive value was 71.4% (Table 5).

Comparison of the results of RAST to those of skin test

If RAST was positive, all of them were positive to skin test, and when RAST was negative, the proportion of negative skin test was 31.3%. Overall, there was a 72.5% agreement between these two tests. The sensitivity of RAST to the skin test was 100%, and the specificity of RAST to the skin test was 31.3%. A positive predictive value of RAST to skin test was 68.6%, and a negative predictive value was 100% (Table 6).

Correlation between skin test and RAST according to the results of HD-BPT

When RAST was negative, 16 out of 29 cases (55.2%) with a positive skin test noted a positive HD-BPT. Twenty four out of 26 cases (92.3%) with more than a RAST class 3 revealed a positive HD-BPT. There was a significant correlation between the reaction criteria on the prick test and the RAST class in the HD-BPT positive group (r=0.56, Y=0.64x + 0.82, Fig. 1).

Correlation between the results of the skin tests and those of RAST according to the group of HD-BPT response

Among 59 positive cases to HD-BPT, early bronchoconstriction response was revealed in 26 (47.1%), dual response in 26 (47.1%), and late response in 7 (11.8%). A significant correlation was found between the results of the skin test and those of RAST in the early response group (r=0.50, Y=0.27x + 0.76), but no correlation existed between these two tests in the dual (r=0.39, Y=−0.01x + 0.68) and late response groups in HD-BPT (r=0.00). An interesting point was that all cases of late response were negative to RAST (Fig. 2).

Comparison of IgE and total eosinophil count in peripheral blood

There were no significant differences between response groups of HD-BPT in total serum IgE, total peripheral eosinophil count and PC50 of methacholine (Table 7). There was no significant correlation between total serum IgE and total peripheral eosinophil count (r=0.35, Y=405.6X + 0.36, Fig. 3). The mean total serum IgE was 518.9 u/ml and the mean of total peripheral eosinophil count was 559.4/mm² in 80 bronchial asthmatics.

Scattergram of total serum IgE according to the results of HD-BPT and RAST

The average serum IgE was 252.6 u/ml in the negative HD-BPT group, and 518.0 u/ml in the positive HD-BPT group. A significant difference exists between these two groups (p<0.05). Also, a significant dif-
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- Positive BPT
- Negative BPT

![Graph showing correlation between prick test and RAST class]

\[ r = 0.56 \]
\[ Y = 0.64X + 0.82 \]

RAST Class

*Fig. 1. Correlation between prick test, RAST and bronchial provocation test of house dust.*

Table 7. Comparison of total serum IgE, eosinophil count and PC_{20} of methacholine according to response of bronchial provocation test of house dust

<table>
<thead>
<tr>
<th>Response of HD-BPT</th>
<th>IgE (u/ml)</th>
<th>TEC ('mm')*</th>
<th>PC_{20} methacholine (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early response</td>
<td>510.5±67.2**</td>
<td>565.5±92.2**</td>
<td>1.3±1.2**</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Late response</td>
<td>492.5±85.4</td>
<td>416.9±76.6</td>
<td>1.3±1.0</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual response</td>
<td>564.6±78.7</td>
<td>619.5±66.2</td>
<td>2.1±1.8</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
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</tbody>
</table>

* Total eosinophil count
** Mean ± S.E.

A difference in serum IgE was found between the negative and positive RAST group with a mean IgE value of 299.6 u/ml in the negative RAST and 597.1 u/ml in the positive RAST group (p<0.01) (Fig. 4).

Correlation between the results of skin test and PC_{20} of methacholine

It appeared that a larger size of wheal and
erythema in the skin test was found in the lower PC_{20} of methacholine. But, there was no significant correlation between wheal size of the prick test and PC_{20} of methacholine (r=0.02, Y=−2.35x+0.04). Also, there was no significant correlation between erythema size and PC_{20} of methacholine (r=−0.17, Y=1.3x−0.01) (Fig. 5).

**DISCUSSION**

Most authorities now agree that bronchial asthma is a disease characterized by hypersensitivity of the airway to various allergenic and non-allergenic stimuli, resulting in paroxysms of wheezy respiration, dyspnea, chest tightness, and cough associated with increased airway resistance (Cade and Pain 1971; Cavanaugh et al. 1971). The reversible airway obstruction, characteristic of asthma, may occur following exposure to various non-specific spasmodic stimuli. The airways of patients with asthma are hyperresponsive to many inhaled irritants, as compared to non-asthmatic persons (Curry 1947).

Walker (1918) proposed an etiologic classification of asthma on the basis of the skin test response which has been in use until recently. He used the terms intrinsic and extrinsic, and hypothesized that the intrinsic group represented a response to internal bacterial sensitivity, and that the extrinsic group was allergic to environmental allergens. Important allergens for extrinsic asthma are house dust-dust mites, pollens, molds, animal epidermals, foods, etc. The most important allergen among inhalant allergens is house
dust. Kern (1921) discussed the importance of house dust as a respiratory allergen, and Van Leeuwan (1922) mentioned mites as a possible antigen in house dust. Mitchell et al. (1969) reported that most patients who show positive skin reactions to house dust extracts also show positive reactions to the extracts of mites and vice versa. In Korea, house dust and dust mites are also very important inhalant allergens (Kang 1973; Whang et al. 1974; Cho et al. 1981; Hong et al. 1982; Kim et al. 1983).

For an evaluation of offending allergens in asthma, there are several diagnostic methods employing in vivo and in vitro tests. The skin test and allergen challenge test as in vivo tests and RAST as an in vitro test are most widely used. The skin test, when used with proper extracts, integrated with the clinical history, and interpreted by an experienced person, can be the most helpful screening test. The reliability of the skin test depends on the allergen used, on the way the extracts are prepared, standardized, stored, and applied, and on how the tests are interpreted.

But even under optimal conditions, there is room for doubt as to the etiologic diagnosis, until the case history is absolutely established in which case the skin
tests may be unnecessary (Aas and Johansson 1971). Therefore, skin tests are superficial in the sensitivity aspect, though frequent and informative. However, the immediate skin test reaction has been the principal diagnostic tool in clinical allergy for many years because of its ease of performance, high degree of reproducibility, and good correlation with in vitro measurement of specific IgE (Imber 1977). With the exception of long term immunotherapy as a treatment of extrinsic asthma, more evidence, other than a skin test, is required for the confirmation of offending allergens.

Since the demonstration by Ishizaka (1966 1968) that skin sensitizing antibodies belonged to the IgE
class of immunoglobulins, many studies have demonstrated a correlation between skin test reactivity and total serum IgE (Stenius and Wide 1969; Loeffler and Cawley 1973; Lee et al. 1982). Brown et al. (1979) mentioned that the mean total serum IgE levels were significantly higher in allergenic than in nonallergenic subjects and were found to be positively correlated with the degree of prick test reactivity. The introduction of in vitro tests for measurement of total and specific serum IgE has permitted correlations to be made between clinical history, skin test and serum IgE value in allergic patients.

The radioallergosorbent test is a test system designed to semiquantitate the amount of circulating allergen specific IgE antibody in blood samples. The allergen, covalently coupled to a paper disc, reacts with the specific IgE antibody in the patient's sera. After non-specific IgE is washed away, radioactively labeled antibodies against IgE are added. Following formation of a complex, the radioactivity of this complex is easily measured in a gamma counter (Johansson and Bennich 1967; Wide et al. 1967). Aas and Johansson (1971) compared the results of the RASTs with those of clinical allergy diagnosis by means of case history, skin tests, and BPTs, and reported that the overall reliability of RAST was 73 percent, and RAST as an in vitro test was found to be a very valuable screening aid prior to a bronchoprovocation test. Also, they reported that the use of RAST, as a supplement to a carefully collected case history and correctly performed and critically evaluated skin tests, made the bronchoprovocation test superfluous in 82 percent of the patients.

Allergen bronchoprovocation is a very important step for the confirmation of etiologic allergens in bronchial asthma. Generally, the indications of the allergen bronchoprovocation test are as follows: 1) elucidation of the role of specific allergens in asthma, 2)
means of comparison for other tests, for example, skin
tests, in vitro tests, and new diagnostic tests, 3) when
skin tests cannot be performed, 4) evaluation of the
therapeutic effect of immunotherapy, 5) evaluation
of new or specific allergens in allergic disease, 6)
evaluation of treatment modality and blocking agents,
and 7) convince the patient of cause and effect rela-
tionships (Rosenthal et al. 1979). But certainly there
are circumstances when the bronchial provocation
test should not be performed: 1) if the patient is
unable to control or reacts to the challenge, 2) if pa-
tient is having an exacerbation of his asthma, 3) dur-
ing upper respiratory or other infections, 4) if the
patient does not have sufficient pulmonary reserve
to tolerate a bronchoprovocation test (Spector and
Farr 1977).

The allergen challenge test takes a long time. And
the allergen challenge test should be done for only
one allergen at a time. Of course, there may be some
serious side effects during challenge test. The
parameters of pulmonary function that can be
evaluated during a challenge test are numerous and
include the FVC, FEV₁, SCL, PEFR, and flow
volume curve. Currently the most widely used
parameter is FEV₁. Bruce et al. (1973) have observed
the correlation between skin tests and bronchial sen-
sitivity in asthma patients, and raised a question con-
cerning the special place of the bronchoprovocation
test in the diagnosis of asthma.

Therefore, the study of clinical correlations among
skin test, RAST, and allergen challenge test in each
allergy laboratory is very important. The agreement
between the bronchoprovocation test and RAST by
Berg and Johansson (1974) was 77 percent, and a
negative prick test corresponded to a negative RAST
in 90 percent. Among the negative prick tests, 5 per-
cent of the patients showed a positive RAST. A
positive RAST was correlated to a positive prick test
in 87 percent. The agreement between positive RAST
and positive BPT was 90 percent, and the agreement
between positive prick test and negative BPT was 37
percent. The agreement between negative RAST and
positive BPT was 27 percent. The correlation between
the positive prick test and RAST increases markedly
with the increased intensity of the skin reaction (Muit-
tari 1976). Stenius and Wide (1969) also found as 83
percent correlation between RAST and the prick test.
A more thorough analysis of the accuracy of RAST
as a diagnostic test, performed by Berg and Bennich
(1971), was that the overall agreement between BPT
and RAST was found to be 74 percent, and that the
relation between RAST and prick test was similar to
that between RAST and BPT.

Park et al. (1981) in Korea reported that the agree-
ment between RAST and the skin test using Der-
matophagoides farinae was overall 79.4 percent. We
showed a 72.5 percent agreement between RAST and
the skin test. Kim et al. (1983) reported HD-BPT in 29
asthmatics. Two out of 11 cases (18.2%) with a
negative skin reaction on the prick test were positive
in HD-BPT. 14 out of 18 cases (77.8%) with a positive
prick test (reaction criteria 2+—4+) were positive in
HD-BPT. There were no cases with a 1+ skin reaction
on the prick test. When compared with our study,
his results of a positive rate of HD-BPT in patients with
a negative skin reaction on the prick test would be
acceptable because he tested more many cases (11
cases) with a negative reaction criteria than we did.

In this paper, we have evaluated the clinical cor-
relation between the skin test, RAST, and bronchial
provocation test of house dust in patients who might
be thought of as house dust asthmatics. For clinical
and practical usefulness in the diagnosis of the offen-
ding allergen, we focused our attention of the reliabil-
ity of the skin test and RAST to the bronchial challenge
test which is thought to be the most confirmative
diagnostic method. According to our results, a positive
probability of HD-BPT in patients who have a positive
prick test and RAST is 87.5 percent. In 29 cases with
a negative RAST but positive prick test of house dust,
there was a positive BPT in 55.2 percent. In that group,
about a half (7/16) of the positive HD-BPT exhibited
a late response only. All 5 cases, which presented an
end point of intradermal test at a 5°—5°×10⁻² dilu-
tion of house dust, displayed a negative HD-BPT.

Considering the above results, we suggest that
asthmatics, who exhibit a positive prick skin test and
RAST of house dust dust mites, do not need to
undergo the bronchoprovocation test, but that for
asthmatics who have a positive skin test and a
negative RAST, the bronchoprovocation test is
necessary for the confirmation of the offending
allergen. Furthermore it will be necessary to further
study the bronchial provocation test in patients who
manifest a weak skin reactivity only to house dust
dust mites among many inhalant allergens.

Additionally we have evaluated the relationship
between nonspecific bronchial hypersensitivity to
methacholine in house dust asthmatics and allergic
skin reactions by size of wheal and erythema to house
dust. Even though Hargreave et al. (1981) reported
some correlation between histamine bronchial
hypersensitivity and wheal size of house dust in
asthma, we did not find any significant correlation be-
tween methacholine bronchial hypersensitivity and skin
reactivity.
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