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Isocyanate-Induced Occupational Asthma : Challenge and Immunologic Studies

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Isocyanate is the most prevalent agent in occupational asthma(OA) in Korea. We analyzed 43 toluene diisocyanate(TDI) induced OA patients of whom 81% were found to be spray painters. The bronchial sensitivity of all subjects was confirmed by TDI-bronchial challenge test. Serum-specific IgE antibodies to isocyanate-human serum albumin(HSA) conjugate were detected by RAST technique(Pharmacia, Sweden). Bronchial challenge test results revealed 21(57%) early, 5 late only, 4 dual, and 12 atypical responders(5 prolonged immediate, 6 square-shaped, 1 progressive). Four(9%) subjects had negative results on the methacholine bronchial challenge test. High levels of serum specific IgE antibody to isocyanate-HSA were found in 17(40%) patients. The prevalence of a specific IgE antibody was not associated with a type of TDI-bronchial challenge test response, smoking and atopic status, presence of rhino-sinusitis and systemic symptoms, or a degree of airway hyperresponsiveness to methacholine($p>0.05$). The period of latency, ranging from 3 to 132 months, was significantly longer in high specific IgE responders($p<0.05$). These data suggest that 40% of isocyanate-induced occupational asthma patients had high specific IgE antibody to isocyanate-HSA conjugate. The presence of specific IgE antibody does not seem to correlate with clinical parameters.

Key Words : *Isocyanate, Asthma, Specific IgE, Isocyanate-human serum albumin, Bronchoprovocation test*

INTRODUCTION

Isocyanates are low-molecular-weight chemicals used in the manufacture of polyurethane forms, varnishes, paints, and plastics. Occupational asthma has been reported among workers exposed to toluene diisocyanate (TDI), methylene diphenyldiisocyanate(MDI), and hexamethylene diisocyanate(HDI)(Musk et al., 1988). These chemicals are currently the most common cause of occupational asthma in Korea(Park et al.,1992) as well as in North America(Cullen and Cherniak, 1989 ; Lagier et al., 1990).

Although considerable controversy remains regarding the pathogenesis of TDI hypersensitivity, several groups of investigators have identified specific IgE antibodies in sensitized workers. The proportion of workers who had positive bronchial challenge results to TDI and detectable specific IgE antibody constituted 0% to 27% of workers(Karol et al., 1978 ; Butcher et al., 1980 ; Karol and Alarie, 1980 ; Danks et al., 1981 ; Baur et al., 1984 ; Pezzini et al., 1984) and 83% of workers sensitized to MDI(Pezzini et al., 1984). These investigators also re-

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ported that 66% of those workers with anti-diisocyanate IgE had an immediate response to bronchial challenge test, suggesting a positive association between serum specific IgE antibody and early asthmatic symptoms.

In the present study, we evaluated the role of specific IgE antibodies to isocyanates in 43 TDI-induced occupational asthma. These data were also analysed according to the length of exposure, latent period, types of asthmatic responses to TDI bronchial challenge tests, and other clinical parameters.

MATERIAL AND METHODS

Subjects

Fourty-three isocyanate-exposed workers, 34 males and 9 females, with a diagnosis of occupational asthma based on their respiratory symptoms and positively to TDI bronchial challenge test, were studied. Sera for specific IgE antibodies were stored at -20℃ until use.

Clinical and functional evaluations

All subjects underwent detailed clinical and occupational history, skin prick tests with common inhalant allergen extracts(Bencard, Bredford, U.K), and pulmonary function tests. All subjects had been free of respiratory infections or exposure to isocyanates for at least one week. No subject took cromolyn, theophylline, sympathomimetics, or antihistamines within the 48 h prior to the challenge study. Forced vital capacity(FVC) and forced expiatory volume in 1 s (FEV1) were measured using a spirometer(Chest, Japan). A subject was considered to be atopic if there was a positive skin reaction to one or more common allergens. Methacholine bronchial challenge test and isocyanate bronchial challenge tests were carried out in all the subjects. The method for the methacholine bronchial challenge test has been described previously(Park et al., 1991). Aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co. Somerset, PA U.S.A) connected to a DeVilbiss dosimeter(DeVilbiss Co. PA. U.S.A) driven by compressed air. Five inhalations of normal saline were taken and thereafter five successively doubled doses of methacholine(0.075 to 25 mg/ml) administered at 5-min intervals until a 20% fall in FEV1 was observed. Methacholine bronchial challenge test was performed on the day before the inhalation challenge with TDI. Methacholine PC20 was determined by interpolation from the dose-response curve. For the TDI bronchial challenge test, the subjects were exposed to TDI(80 : 20 = 2, 4-diisocyanate form : 2,6-diisocyanate form, Aldrich, Milwaukee) through tidal breathing method until asthmatic symptoms were provoked for up to a maximum of 15 min. The concentration of TDI, as measured by TLD-1, a toxic gas detector with chemkey(MDA Scientific, USA), was 20 ppb. FEV1 and maximum mid-expiatory flow (FEF 25-75%) were measured by a spirometer(Chest, Japan) immediately before and after TDI exposure. The FEV1 and maximum mid-expiatory flow rate were measured every ten minutes during the first hour, and these parameters were measured every hour for seven hours after the challenge. Using the classification of Zammit-Tabona et al.(1983), BPT results were categorized as early, late-only, dual, progressive, prolonged immediate, or square-shaped. All subjects gave their written informed consent as required by Ajou University Hospital, Suwon, Korea.

Determination of specific IgE to isocyanate-human serum albumin conjugate

To detect specific IgE antibody to three isocyanates [TDI, MDI, HDI-human serum albumin(HSA) conjugates], radioallergosorbent test(RAST) was performed according to manufacturer's instructions of the Phadebas RAST system(Pharmacia, Diagnostics, Uppsala, Sweden). Paper disks were bound with isocyanate-HSA conjugate and each disc was incubated with 50 ul of the patient's serum for 6 hours at room temperature. The disks were washed three times with 2.5 ml of 0.9% NaCl containing RAST washing additives(Pharmacia, Uppsala, Sweden). Subsequently, 50 ul of ^{125}I-labeled anti-human IgE(Pharmacia) were added to each disk and left for 18 hours at room temperature. The disk were washed again, and the bound ^{125}I was measured with a gamma counter. All assays were performed in duplicate. The results were expressed as a ratio of the mean counts per minute(mcpm) of allergen disc to mcpm of HSA disc. A ratio of higher than 2 was considered a positive test result.

Statistical Analysis

Statistical analysis of variance and non-parametric unpaired test(SPSS version 6.0, Chicago, IL) were applied to compare all the parametrs between two groups.

RESULTS

Early asthmatic response was the most common reaction(51.2%) to the TDI-bronchoprovocation test. Late only asthmatic response was noted in 5 patients

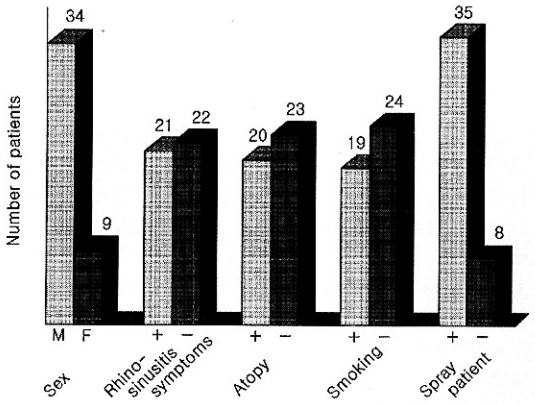

Fig. 1. Clinical features of the study subjects. (M : male, F : female)

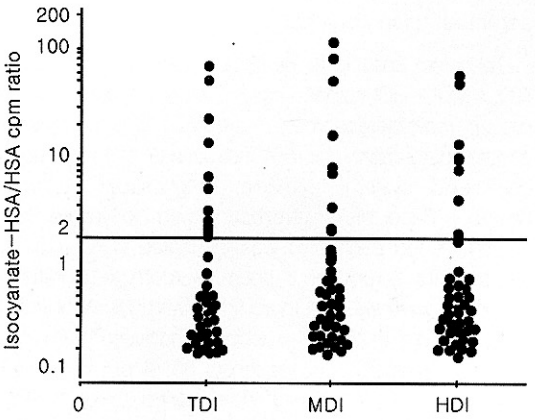

Fig. 2. Specific IgE binding to toluene diisocyanate(TDI), diphenylmethan isocyanate(MDI) and hexamethylene diisocyanate (HDI)

(11.6%), dual in 4(9.3%), prolonged immediate in 5 (11.6%), square-shaped in 6(14%), and progressive asthmatic response in one patient.

There was a slight predominance of non-atopic subject(Fig. 1). Rhinosinusitis symptoms were seen in 21 patients(48.8%). Four subjects(9.3%) complained of systemic symptoms such as febrile sensation or arthralgia with exposure to isocyanates. Mean duration of exposure to isocyanates was 61.6 months ; the range was 3 to 240 months. The latent period ranged from 3 to 234 months(mean : 40.8 months), and symptom duration ranged from 1 to 12 months (mean : 9.7 months).

High specific IgE antibody to three isocyanates(TDI and/or MDI and/or HDI) was detected in 17 patients (39.5%) ; and the level covered a wide spectrum, ranging from 2 to 67.4(Fig. 2). Among eleven patients who had high specific IgE antibodies to MDI and/or HDI, nine had high TDI-specific IgE antibody. Five had only TDI-specific IgE antibody.

When high and low specific IgE responders were compared(Table 1), no differences were found between either type of asthmatic responses and symptom duration, atopic status, smoking habits, or presence of systemic and rhinosinusitis symptoms($p>0.05$). The latent period was significantly longer in high IgE responders ($p<0.05$). Early asthmatic response in TDI-bronchoprovocation was not associated with the presence of specific IgE antibody($p>0.05$).

DISCUSSION

In this study, we analyzed the clinical features of isocyanate-induced occupational asthma. The majority of cases were male workers and spray painter was the most common occupation category. There was a wide range of exposure period and latent period from 3 to

Table 1. Comparison of clinical parameters between high and low IgE responders

Clinical profile	High IgE responder (n=17)	Low IgE responder (n=26)	P value
Symtom duration(m)	7.8±5.4*	10.9±8.2*	0.15
Exposure duration(m)	79.0±55.1	50.2±28.2	0.09
Latent period(m)	69.8±56.7	38.5±25.9	0.04
Atopy(%)	9(53.5)	11(39.5)	0.50
Rhinosinusitis symptoms(%)	7(41.2)	14(53.8)	0.42
Smoking habits(%)	7(41.2)	12(46.2)	0.75
Systemic symptoms(%)	3(17.6)	1(3.8)	0.13
Early asthmatic responders(%)	10(58.8)	12(46.2)	0.42

m : month * : mean±SD
Atopy is defined as a positive reactor to more than one common inhalant allergen on skin prick test

240 months, from 3 to 234 months respectively. 39.5% of the subjects had high specific IgE to isocyanate-HSA conjugates, a finding which is relatively higher than in other studies(Karol et al., 1978 ; Butcher et al., 1980 ; Karo l and Alarie, 1980 ; Danks et al, 1981 ; Baur et al., 1984 ; Pezzini et al., 1984). The reason why some people become IgE-sensitized to TDI-HSA, while others who work in the same environment remain unsensitized, is not clear.

Serologic and bronchial cross reactivity among these three isocyanate-HSA conjugate has been reported (Baur, 1983). In this study, most positive reactors on TDI-HSA had a concurrent positive reaction to MDI-and HDI-HSA RAST conjugates. A comparison of high and low specific IgE responders yielded the interesting finding that latent period and exposure duration were significantly longer in high IgE responders. When we observed these patients for more than 2 years, a favorable prognosis was noted among high specific IgE responders(unpublished data).

The atypical asthmatic response to isocyanate bronchoprovocation test has indeed been classified by some investigators(Zammit-Tabona et al., 1983). In this study, early asthmatic response was the most frequently observed type, while(34.3%) 12 had atypical asthmatic responses such as prolonged-immediate, square-shaped, or progressive. Immediate bronchoconstriction after allergen inhalation is induced by IgE-mediated reaction(Hong and Park, 1989 ; Park et al, 1989). Pezzini et al.(1984) reported the association between early asthmatic reaction to isocyanate inhalation challenge testing, and the reaction of specific IgE antibody to isocyanate-HSA conjugate. In our study, the presence of isocyanate-specific IgE antibody was not related to immediate bronchoconstriction. Other pathogenetic mechanisms might help to induce various asthmatic responses to isocyanate.

IgE-sensitization to low molecular-weight occupational allergens has been associated with smoking habits.(Venables et al.,1985 ; Chan-Yeung,1986 ; Park et al., 1991). Our previous report suggested no association between the presence of specific IgE to TDI, and atopy or smoking habits(Park et al.,1992). In this study, nearly half of the patients had atopy. Two showed a positive response on the allergen challenge test. Our result suggests that isocyanate induced occupational asthma could be found whether they are atopic or not and atopic status and smoking habits do not contribute to the development of specific IgE sensitization to isocyanate-HSA conjugates.

Four subjects showed a negative result on methacholine bronchial challenge testing. Their airway hyperresponsiveness to methacholine developed after the isocyanate bronchoprovocation test. As suggested by previous studies, some isocyanate-induced occupational asthma occur without airway hyperresponsiveness (Fink and Schleuter, 1978 ; Hargreave et al., 1980 ; Stanescu and Frans, 1982 ; Park et al, 1992). This study underscores the need for careful inquiry about a patient's respiratory symptoms in the workplace in order to identify occupational asthma. Absence of airway hyperresponsiveness does not necessarily preclude occupational asthma.

In this study, 40% of isocyanate-induced occupational asthma had specific IgE antibody to isocyanate-HSA conjugates. The presence of specific IgE antibody was not associated with any clinical parameters. Longer latent period might be needed for IgE-mediated sensitization to isocyanate.

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