Journal of Korean Medical Science
Vol 7, No. 2, 122-127 June 1992

Clinical and Immunological Evaluation of Isocyanate-Exposed Workers

Hae Sim Park[1], M.D., Jae Nam Park[1]., M.D.,
Jae Won Kim[1], M.D., Soo Kun Kim,[2] M.D.

Department of Chest Medicine[1] National Medical Center, Bok Ji Clinic[2] Seoul, Korea

Isocyanates are the most significant cause of occupational asthma in our country. To evaluate the prevalence of work-related respiratory symptoms and immunologic sensitization to it, we performed a questionnaire survey, allergy skin test, radioallergosorbent test (RAST) to toluene diisocyanate (TDI)-human serum albumin (HSA) conjugate and methacholine bronchial challenge test on 23 isocyanate-exposed employees and 9 unexposed controls working in a zipper factory.

Six employees (26.1%) complained of work-related respiratory symptoms and three symptomatic workers showed significant bronchoconstrictions on TDI-bronchoprovocation test. Three (13%) asymptomatic workers had high specific IgE antibodies to TDI-HSA and none of the TDI-sensitive asthmatic workers had specific IgE antibody. One of the TDI-sensitive asthmatic workers showed a negative result on the initial methacholine bronchial challenge test, but bronchial hyperresponsiveness developed after the TDI challenge.

It was suggested that TDI-sensitive asthma was noted in three (13%) of 23 exposed workers and that asymptomatic workers could have high specific IgE antibody. Measurement of the changes in bronchial hyperresponsiveness after the TDI challenge could be helpful to diagnose TDI-sensitive asthma.

Key Words: *Isocyanate, Occupational Asthma, Bronchial Hyperresponsiveness, Specific IgE*

INTRODUCTION

Isocyanates are used in the manufacture of numerous products, including insulation, foam filling for furniture and polyurethane paints. Important isocyanates include toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI), and diphenylmethane diisocyanate (MDI), all of which can polymerize with compounds containing active hydrogen atoms. There have been a number of pulmonary reactions attributed to TDI including bronchial asthma (Maxon, 1964; Munn, 1965; Pepys et al., 1972; Charles et al., 1976; Fink and Schleuter, 1978; Park et al., 1991). Estimates of the incidence of asthma or chronic obstructive pulmonary disease in isocyanate workers have ranged from 5 to 30% (US Department of Health, Education, and Welfare, 1973; Baur et al., 1984). Isocyanates have also been described as causing allergic rhinitis, allergic conjunctivitis, and hypersensitivity pneumonitis. (Zeiss et al., 1980; Bernstein, 1982; Baur et al., 1984).

Studies on the pathogenesis of isocyanate asthma have yielded conflicting results. Immunologic reactions were suggested by several authors (Butcher et al., 1976; Bernstein, 1982; Grunewalder and Karol, 1986; Wass and Belin, 1989). Other mechanisms have been suggested by other investigators. (Butcher et al., 1977; Davies et al., 1977; Butcher et al., 1979).

In this study, to determine the prevalence of immunologic sensitization, work-related respiratory symptoms, and the relationship of immunologic sensitization to work-related respiratory disease, we performed a questionnaire survey and skin test, RAST, methacholine bronchial challenge test and TDI-bronchoprovocation test in 23 workers exposed to TDI and nine unexposed workers as controls in a zipper factory.

Address for correspondence: *Hae Sim Park, Department of Chest Medicine National Medical Center Jungku Eulgiro 6-ka 18-79 Seoul, Korea, Tel: 260-7281.*

MATERIALS AND METHODS

The study population consisted of 23 factory workers

who spray-paint zippers using paints that contain TDI. The job categories of the workers were paint mixers and spray painters. Nine employees who worked in another section of the same factory and who made buttons, participated as controls. Their sera were collected and stored at −20°C.

Questionnaires

Initially, doctors administered a questionnaire, which was a National Heart and Lung Institute, modification of the British Medical Research Council questionnaire (1966), with additional questions asked later at each visit. In evaluating and comparing these data, the following definitions were used: Lower respiratory symptoms referred to cough, sputum, chest tightness or shortness of breath. Symptomatic employees were those workers who had suffered from lower respiratory symptoms during and after the work.

Allergy Skin test

Skin prick tests with eight common inhalant allergens (alder, oak, rye grass, ragweed, mugwort, aspergillus spp. Dermatophagoides farinae, cat fur, histamine (1mg/ml), Bencard Allergy Unit, Brentford, Middlesex, England) and 2,4-TDI (Junsei chemical Co. Japan) were performed on the volar side of both forearms simultaneously. The reactions were read 15 minutes later. When the wheal size was more than 2 mm and erythema size was more than 21mm, it was read as 2+. Atopy was defined as a positive reactor (≧2+) to more than one common inhalant allergens on skin prick test.

Methacholine bronchial challenge test

Airway hyperresponsiveness was determined by the previously described standard method (Chai et al., 1975) in all employees. An aerosol of 0.9% NaCl, followed by serial doubling concentrations of methacholine (0.075 to 25 mg/ml), was inhaled. The FEV1 was measured 5 minutes after each inhalation until the FEV1 had fallen by 20% from the postsaline basal value. It was determined that nonspecific bronchial reactivity was present if a patient demonstrated more than a 20% decrease in FEV1 after inhalation of any concentration (0.075 to 25 mg/ml) of methacholine. The PC20 level was obtained from the dose-response curve.

Bronchoprovocation test with TDI

The bronchoprovacation test was performed according to the previous study (Park et al. 1990). A phenolized saline solution was inhaled ten times using tidal breathing from a nebulizer 646 (Devilbiss Co. Somerset, Penn.) with a compressed air source. In the case of the TDI bronchial challenge test, the subject was asked to breathe the smell from the TDI solution contained in a large beaker ten times using tidal breathing. The forced expiratory volume in one second (FEV1) and maximum mid expiratory flow (FEF25-75%) were measured with a spirometer (HI 298, Japan) before and 10 minutes after inhalation. Then, the FEV1 and maximum mid expiratory flow were measured frequently during the first hour, and pulmonary function tests were performed every hour for seven hours after the challenge.

RAST to TDI-Human serum albumin conjugate

To detect specific IgE antibody to TDI-human serum albumin (HSA) conjugate, RAST was performed according to the guidance of the Phadebas RAST system (Pharmacia, Diagnostics, Uppsala, Sweden). The paper disc bound with TDI-HSA conjugate and the HSA disc were incubated with 50 ul of each 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). Then, 50 ul of 125-I-labeled anti-human IgE (Pharmacia) was added to each disk and left for 18 hours at room temperature. The disks were washed again, and the bound 125-I was measured with a gamma counter. All assays were performed in duplicate. The results were expresed as a ratio of the mean counts per minute (mcpm) of allergen disc to mcpm of HSA disc. A ratio of 2 or higher was regarded as a positive test result.

RESULT

Response to the survey

The questionnaire data were summarized in Table 1. Six employees (26.1%) complained of lower respiratory symptoms with or without nasal symptoms during and after working. None of the unexposed employees had work-related respiratory symptoms. Two (8.8%) employees had nasal symptoms only. When the methacholine bronchial challenge tests were performed on all the exposed employees, two (33.3%) symptomatic employees and one (7.1%) asymptomatic employee had non-specific bronchial hyperreactivity.

Bronchoprovocation test with TDI

When bronchoprovocation tests were performed on six symptomatic and one asymptomatic employee with

Table 1. Results of work-related symptoms, methacholine bronchial challenge test and RAST in 23 exposed workers.

	Number of Employees (% total)	Methacholine Bronchial Challenge Test (%)	Specific IgE Antibody (%)
Lower respiratory symptoms	6 (26.1)	2/6 (33.3)	0 (0)
Respiratory symptoms alone	5 (21.7)	1/5 (20.0)	0 (0)
Plus nasal symptoms	1 (4.3)	1/1 (100.0)	0 (0)
Nasal symptoms alone	2 (8.7)	0 (0)	0 (0)
Skin symptoms	1 (4.3)	0 (0)	0 (0)
No work related symptoms	14 (60.9)	0 (0)	0 (0)

Lower respiratory symptoms: cough, sputum and shorteness of breath
Nasal symptoms: rhinorrhea, sneezing and congestion
Skin symptoms: urticaria and pururitus

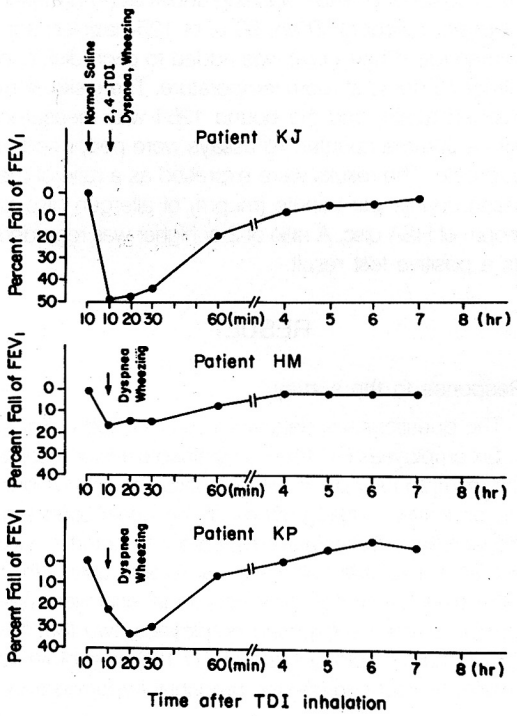

Fig. 1. Result of bronchoprovocation test with 2,4-toluene diisocyanate (TDI) in three TDI-sensitive asthmatic workers in the laboratory.

non-specific bronchial hyperreactivity, three symptomatic employees showed significant bronchoconstrictions, as shown in Fig 1.

Table 2 shows the clinical characteristics of the three TDI-sensitive asthmatic workers. All of them showed early asthmatic responses. None of them had specific IgE antibody to TDI-HSA and were atopic status. Two of them had non-specific bronchial hyperreactivity, but one showed a negative result on the initial methacholine bronchial challenge test. The following methacholine bronchial challenge test revealed that the bronchial hyperresponsiveness developed 1 day after the TDI challenge (PC20:0.6 mg/ml), which continued until the 7th day and returned to 25 mg/ml on the 14th day (Fig 2).

Specific IgE antibody to TDI-HSA

Fig. 3 illustrates the specific IgE binding on TDI-HSA disc in all employees. The cut-off value of the positive result was determined as 2. Three (13.0%) exposed workers showed high specific IgE binding and all of them were asymptomatic employees. None of the unexposed workers had specific IgE antibody. No association was found between specific IgE antibody and smoking status (Table 3).

Table 2. Clinical characteristics of 3 toluene diisocyanate (TDI)-sensitive asthmatic workers

Patient	Age	Exposure Duration (Months)	Smoking Status	Atopy	Specific IgE to TDI	Methacholine PC20 (mg/ml)	TDI-Bronchoprovocation test
KJ	39	60	Former smoker	Absence	Absence	1.25	Early Response
HM	30	24	Non-smoker	Absence	Absence	10.0	Early Response
KP	38	85	Current smoker	Absence	Absence	Negative	Early Response

Atopy was defined as a positive reactor to common inhalant allergens on skin prick test

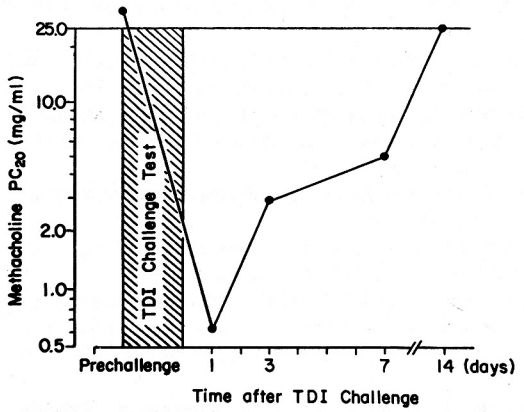

Fig. 2. Changes of bronchial responsiveness to methacholine before and after toluene diisocyanate (TDI)-bronchial challenge test in KP patient.

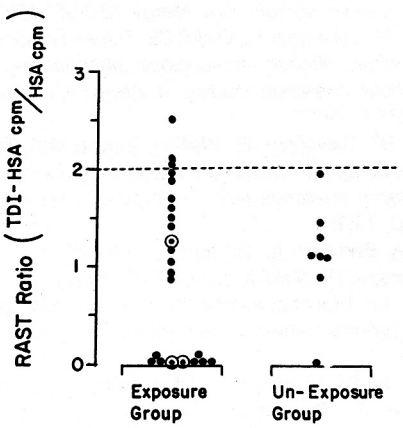

Fig. 3. Radioallergosorbent test (RAST) ratios of toluene diisocyanate (TDI) in exposed and unexposed workers. HSA=human serum albumin. @ TDI induced asthmatic workers.

Table 3. The association between smoking status and specific IgE antibody to toluene diisocyanate (TDI)-human serum albumin (HSA) conjugate

Smoking Status	Specific IgE to TDI-HSA	
	Absent	Present
Non smoker	11	2
Ex smoker	4	1
Current smoker	5	0

: $P>0.05$

DISCUSSION

Prevalence of lower respiratory symptoms that could be related to isocyanate exposure is 26.1% in this study. TDI-induced asthma was noted in three cases (13%) which was higher than those of other investigators (Brooks, 1977; Butcher et al., 1983). Bronchial hyperresponsiveness unrelated with isocyanate was noted in one case.

In the area of TDI asthma, the portion of workers with positive inhalation challenge who have specific IgE detectable by in vivo or in vitro means has been reported by some investigators to be less than 20% (Butcher et al., 1976; Baur and Fruhmann, 1982). Bauer et al. (1984) reported a similar proportion (14%) of syptomatic workers having specific IgE but also emphasized that virtually no asymptomatic worker had specific IgE. Another group of investigators (Pezzini et al. 1984) reported the presence of anti-diisocyanate IgE in 27% of TDI workers with positive bronchial provocation challenge and in 83% of MDI workers with positive challenge. Cartier et al. (1989) reported that there was a loose association between the results of the isocyanate challenge test and the levels of specific IgE, but the association was much better with the level of

specific IgG.

In most cases of occupational asthma induced by low molecular weight compounds, the compounds act as haptens and combine with a protein carrier to act as allergens (Chan Yeung, 1986). Isocyanates, such as TDI and HDI, by virtue of their high degree of reactivity, appear to alter the native structure of the carrier protein to the extent that both haptenic and new antigenic determinants could be determined (Chen and Bernstein, 1982; Baur, 1983). In this study, we have used RAST to detect TDI-specific IgE antibody in their serum. By use of this test, specific IgE antibodies were detected in 13.3% of all exposed workers, all of whom were asymptomatic workers. Some investigators (Venables et al, 1985; Chan Yeung, 1986) including our previous study of reactive dye asthma (Park et al., 1991) reported that there was an association between smoking and specific antibodies production to low molecular weight chemicals. In this study, no association was found between smoking and specific IgE antibody to TDI-HSA. Two of the three TDI-asthma cases were smokers. None of the three TDI-sensitive asthma cases had specific IgE to TDI-HSA conjugate. It was suggested that these findings might indicate the involvement of other, nonimmunologic mechanisms in the induction of hypersensitivity to these subjucts, and that asymptomatic workers could have specific IgE antibody.

The majority of patients with symptomatic occupational asthma had demonstrable non-specific bronchial hyperreactivity (Lams et al. 1979). Some investigators have reported several cases of occupational asthma caused by TDI without non-specific bronchial hyperreactivity (Fink and Schleuter, 1978; Hargreave et al., 1980; Stanescu and Frans, 1982; Park et al., 1990). In this study, one case of TDI- sensitive asthma who showed a negative response on the initial methacholine bronchial challenge test which was performed before the TDI bronchoprovocation, was noted among three cases of TDI-asthma. The subsuquent methacholine bronchial challenge test revealed that bronchial hyperresponsiveness developed 24 hours after the TDI challenge, this continued until the 7th day and returned to 25 mg/ml on the 14th day. And also, isolated immediate asthmatic reactions could induce significant changes in methacholine PC20 as several investigators have already reported (Fabbri et al, 1987; Malo et al., 1989; Park et al., 1990). It was suggested that careful inquiry about whether the patient has ever experienced respiratory symptoms at his/her workplace is needed to identify TDI-induced occupational asthma patients, and a negative methacholine challenge result cannot be used to exclude occapational asthma. And, measuring the changes of bronchial hyperresponsiveness after the TDI challenge might be helpful in diagnosing TDI-induced occupational asthma.

In summary, TDI asthma was noted in 3 out of 23 exposed workers and specific IgE to TDI-HSA was detected in three of them, all of whom were asymptomatic workers.

REFERENCES

Baur X: *Immunological cross-reactivity between different albumin-bound isocyanates. J Allergy Clin Immunol 71:197-205, 1983.*

Baur X, Dewair M, Frushmann G: *Detection of immunologically sensitized isocyanate workers by RAST and intracutaneous skin tests. J Allergy Clin Immunol 73:610-8, 1984.*

Baur X, Fruhmann G: *Specific IgE antibodies in patients with isocyanate asthma. Chest 80 (suppl): 73, 1981.*

Bernstein IL: *Isocyanate-induced pulmonary diseases. A current prospective. J Allergy Clin Immunol 70:24-31, 1982.*

British Medical Research Council questionnaire on respiratory symptoms, 1966.

Brooks SM: *Bronchial asthma of occupational origin. Scan J Work Environ Health 3:53-72, 1977.*

Butcher BT, Karr RM, O'Neil CE: *Inhalation challenges and pharmacologic studies of toluene diisocyanate (TDI)-sensitive workers. J Allergy Clin Immunol 64:146-52, 1979.*

Butcher BT, O'Neil CE, Reed MA, Salvaggio JE: *Radioallergosorbent testing of toluene diisocyanate-reactive individuals using p-tolyl isocyanate antigen. J Allergy Clin Immunol 66:213-6, 1980.*

Butcher BT, O'Neil CE, Reed MA, Salvaggio JE: *Radioallergosorbent testing with p-tolyl monoisocyanate in toluene diisocyanate workers. Clin Allergy 13:31-5, 1983.*

Butcher BT, Salvaggio JE, O'Neil CE: *Toluene diisocyanate pulmonary disease: Immunologic pharmacologic and mecholyl challenge studies. J Allergy Clin Immunol 59:223-7, 1977.*

Butcher BT, Salvaggio JE, Weill H, Ziskind MM: *Toluene diisocyanate (TDI) pulmonary disease; immunological and inhalation challenge test. J Allergy Clin Immunol. 58: 9-100, 1976.*

Cartier A, Bernstein IL, Burge PS, Cohn JR, Fabbri LM, Hargreave FE, Malo JL, Mckay RT, Salvaggio JE: Guidelines for bronchoprovocation in the investigation of occupational asthma. J Allergy Clin Immunol 84:823-8, 1989.

Chai H, Farr RS, Froelich LA, Mathison DA, Rothenthal RR, Shelter AL, Spector SL: *Standardization of bronchial challenge procedure. J Allergy Clin Immunol 56:323-7, 1975.*

Chan-Yeung: *Occupational asthma. Am Rev Respir Dis 133:686-703, 1986.*

Charles J, Bernstein A, Jones B: *Hypersensitivity pneumo-*

nitis after exposure to isocyanates. Thorax 31:127-136, 1976.

Chen SE, Bernstein IL: *The guinea pig model of diisocyanate sensitization. I Immunologic studies. J Allergy Clin Immunol 70:383-92, 1982.*

Davies RJ, Butcher BT, O'Neil CE, Salvaggio JE: *The in vitro effect of toluene diisocyanate on lymphocyte cyclic adenosine monophosphate production by isoproterenol, prostaglandin and histamine. A possible mode of action. J Allergy Clin Immunol 60:223-9, 1977.*

Fabbri LM, Boschetto P, Zocca E, Milani G, Pivirotto F, Plebau M, Burlina A, Licata B, Mapp CE: *Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. Am Rev Respir Dis 136:36-42, 1987.*

Fink JN, Schleuter DR: *Bathtub refinisher's lung: An unusual response to toluene diisocyanate. Am Rev Respir Dis 118:955-9, 1978.*

Grunewalder E, Karol MH: *Nitrocellulose-based RAST to detect IgE antibodies in workers hypersensitive to diphenylmethane-4, 4'-diisocyanate. Allergy 41:203-9, 1986.*

Hargreave FE, Ramsdale EH, Pugsley SO: *Occupational asthma without bronchial hyperresponsiveness. Am Rev Respir Dis 131:513-5, 1980.*

Karol MH, Ioset MH, Alarie YC: *Tolyl-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. Am Ind Hyg Assoc J 39:454, 1978.*

Lam S, Wong R, Chan-Yeung M: *Nonspecific bronchial reactivity in occupational asthma. J Allergy Clin Immunol 63:28-34, 1979.*

Malo J-L, L'Archeveque J, Cartier A: *Significant changes in nonspecific bronchial responsiveness after isolate immediate bronchospecific responsiveness caused by isocyanate, but not after a late reaction caused by plicatic acid. J Allergy Clin Immunol 83:159-64, 1989.*

Maxon FC Jr: *Respiratory irritation from toluene diisocyanate. Arch Environ Health 8:755-8, 1964.*

Munn A: *Hazards of isocyanates. Ann Occup Hyg 8:163-9, 1965.*

Park HS, Cho YS, Lim YS, Rhu NS, Cho DI, Kim JW, Kim SK: *A case of occupational asthma with systemic illness due to toluene diisocyanate (TDI) and diphenyl methane diisocyanate (MDI). J Kor Soc Allergor 11:70-5, 1991.*

Park HS, Cho YS, Park JN, Baik JH, Rhu NS, Cho DI, Kim JW: *Significant changes of bronchial responsiveness to methacholine after early asthmatic reaction to toluene diisocyanate (TDI) in a TDI-sensitive asthmatic worker. J Kor Med Sci 5:185-8, 1990.*

Park HS, Lee MK, Kim BO, Lee KJ, Roh JH, Moon YH, Hong CS: *Clinical and immunological evaluations of reactive dye-exposed workers. J Allergy Clin Immunol 87: 639-49, 1991.*

Pepys J, Pickering CAC, Bredin ABX, Terry DJ: *Asthma due to inhaled chemical agents-toluene diisocyanate. Clin Allergy 2:225-36, 1972.*

Pezzini A, Riviera A, Paggiar P, Spiazzi A, Gerosa F, Filieri M, Toma G, Tridente G: *Specific IgE antibodies in twenty-eight workers with diisocyanate-induced bronchial asthma. Clin Allergy 14:453-61, 1984.*

Stanescu DC, Frans A: *Bronchial asthma without increased airway reactivity. Eur J Respir Dis 63:5-12, 1982.*

US Department of Health, Education and Welfare: *Occupational exposure to toluene diisocyanate. Washington D.C: US Government printing office. 1973.*

Venables KM, Topping MP, Howe W, Luczynska CM, Hawkins R, Newman Taylor AJ: *Interaction of smoking and atopy in producing specific IgE antibody against a hapent protein conjugate. Br Med J 290:201-4, 1985.*

Was U, Belin L: *Immunologic specificity of isocyanate induced IgE antibodies in serum from 10 sensitized workers. J Allergy Clin Immunol. 83:126-35, 1989.*

Zeiss CR, Kanellakes TM, Bellone JD, Levitz D, Pruzansky JJ, Patterson R: *Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyante (MDI) exposure. J Allergy Clin Immunol 5:346-52, 1980.*