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Original Article

Study on Allergic Rhinitis in Workers Exposed to Methyltetrahydrophthalic Anhydride

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Abstract

Methylterahydrophthalic anhydride (MTHPA) is used as a hardening agent in an epoxy resin system. Because work-related nasal symptoms were observed in some workers exposed to MTHPA at two condenser plants, a cross-sectional survey was performed to improve their work environment. Mean MTHPA levels in the manufacturing processes to which the workers were routinely assigned were extremely low (1.09-22.4 $\mu g/m^3$). However, specific IgE antibody (S-IgE) was detected in 9 (32%) of 28 workers. Of these, 8 (89%) had nasal symptoms. An IgE-mediated mechanism seems to be associated with at least some of the cases of work-related nasal symptoms. This indicates that the occupational health administration of MTHPA cannot be controlled simply by limiting exposure in the work environment. Total IgE (T-IgE) levels were significantly higher in S-IgE-positive workers than in S-IgE-negative workers (geometric mean, 200.5 and 51.3 IU/ml, respectively; $p<0.002$, unpaired t test). These findings demonstrate that workers in whom S-IgE is less likely to be produced, i.e., those in whom the T-IgE level is 80 IU/ml or less, should be assigned to work in these manufacturing processes.

Key words: Allergic rhinitis, Methyltetrahydrophthalic anhydride, Specific IgE, Specific IgG4, Total IgE

Introduction

Epoxy resin hardening agents, which cause contact dermatitis, are among the allergens frequently found in the industrial environment[1]. In 1976, the Labor Ministry of Japan issued Notification No.442, "Prevention of health hazards due to epoxy resin hardening agents". As a result of this notification, a shift from highly toxic amine compounds to less toxic acid anhydrides was made. However, acid anhydrides have also been known to cause allergic symptoms; specific IgE antibody was detected in patients with occupationally incurred asthma at a plastics plant for the first time in 1976[2].

Methyltetrahydrophthalic anhydride (MTHPA) is used as a hardening agent in an epoxy resin system for electric insulation and proteciton in the manufacturing of condensers. Some workers at two plants engaged in the manufacturing process had work-related nasal symptoms (sneezing, secretion, and blockage). Because exposure to MTHPA has been associated with work-related nasal symptoms[3], we examined the relationship of MTHPA exposure to these symptoms in a group of 28 workers in these plants in June and July 1994.

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Material and methods

Plants and subjects. In the two condenser plants investigated, the manufacturing process consisted of soaking and hardening (100 ℃: Zone 1), powder coating (Zone 2), cutting (Zone 3), and finishing (Zone 4). The zones were separated by a partition and doors to prevent contamination by the MTHPA vapor generated in Zone 1. Twenty-five workers (all male; mean age, 31 years; range, 19-50) at the plants had a median work experience of 4 years (range, 0.25-14). Nine o f the 25 workers were routinely assigned to monitoring work in Zone 3, and 16 in Zone 4. Nonroutine operations included cleaning of the MTHPA soaking bath (2-5 times/ week, about 90 min each time; rubber gloves and a gas mask were worn). Sixteen of the 25 workers were assigned to cleaning. Three former workers (all male; mean age, 42 years; range, 30-57), who had a median work experience of 4 years (range, 3-5) in Zone 3 or Zone 4 of one of the plants, were included in the study. These men had been out of exposure for a median 7 years (range, 5-20) and develop nasal symptoms even

today when they participate in these processes for 10-30 min.

Work-related nasal symptoms. The subjects completed a simple questionnaire about their ocular and nasal symptoms. Nasal symptoms were defined as attacks of sneezing, secretion, and blockage, with recovery either on weekends or on holidays, that started after joining the plant. A physician (KY) took a brief medical history concerning the symptoms and their relation to work.

Air sampling and analysis. MTHPA levels in air were determined by area sampling on silica gel tubes, and the anhydride was analyzed by gas chromatography [4]. The detection limit was 1.0 $\mu g/m^3$ in a 20-1 air sample. MTHPA levels in air have been measured in these plants every 6 months since 1993.

Antibody determinations. MTHPA conjugate was prepared by the method of Welinder et al [5]. The molar ratio of human serum albumin (HSA) to MTHPA in the conjugate was 1:18-22 [6]. Specific IgE antibody (S-IgE) to the conjugate was measured with a Pharmacia CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden). The results were expressed as U/ml, and the detection limit was 0.35 U/ml. Specific IgG4 antibody (S-IgG4) to the conjugate was analyzed by the EIA assay (Vector Laboratories Inc., Burlingame, CA, USA) [5]. The results were expressed as the absorbance value. Total IgE (T-IgE) levels were measured by the CAP system according to the manufacturer's instructions.

Statistical methods. For comparison of the difference in T-IgE between the S-IgE-negative and S-IgE-positive groups, the unpaired t test was used on log-transformed values.

Results

In the two plants, the mean MTHPA level was highest in Zone 1 (762-988 $\mu g/m^3$), followed by Zone 2 (43.1-175 $\mu g/m^3$), Zone 3 (1.09-22.4 $\mu g/m^3$), and Zone 4 (1.29-11.5 $\mu g/m^3$); thus, the level decreased with increasing distance from the source of MTHPA.

As shown in Table 1, S-IgE was positive in 9 (32%) of the 28 subjects. Three of these 9 subjects had nasal and ocular symptoms, and 5 had nasal symptoms. The S-IgE-positive group had a geometric mean of 3.66 U/ml (range, 0.49-10.9 U/ml).

Total IgE levels in S-IgE-negative group were low (geometric mean, 51.3; range, 9.30-376 IU/ml), whereas most of the subjects in the S-IgE-positive group had T-IgE levels of >80 IU/ml (geometric mean, 200.5; range, 70.2-463 IU/ml). The difference between the T-IgE levels in the two groups was highly significant ($p<0.002$) (Fig 1).

Table 1. Relationships between specific antibodies and nasal symptoms.

n=28	S-IgE*	S-IgG4#
SS (n=8)	8	4
SN (n=1)	1	1
NS (n=2)	0	1
NN (n=17)	0	2

*: S-IgE level >0.35 U/ml

#: S-IgG4 was defined as positive if the level exceeded 2× (Mean+3SD) in controls, i.e. 0.020. Ten medical students (all males) served as controls.

SS: IgE-sensitized symptomatic group, SN: IgE-sensitized nonsymptomatic group, NS: IgE-nonsensitized symptomatic group, NN: IgE-nonsensitized nonsymptomatic group.

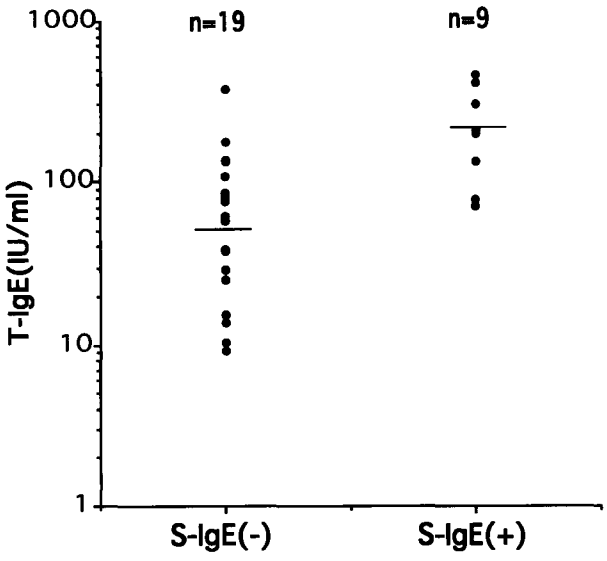

Fig 1. Total IgE levels in workers with or without S-IgE against MTHPA-HSA conjugate. S-IgE (-): S-IgE-negative group, S-IgE (+): S-IgE-positive group. Horizonatal bars are geometric mean values.

Discussion

MTHPA has irritating effects on the mucous membranes and has sensitizing properties, causing symptoms in the eyes and airways [3, 5]. In a nasal challenge test, the association of the S-IgE antibody against MTHPA-HSA with work-related nasal symptoms has been reported [7]. Even if allergic rhinitis is not considered to be as serious as asthma, it can be troublesome for many workers. Moreover, allergic rhinitis may precede occupationally incurred asthma [8]. Thus, it is important to clarify whether allergic mechanisms are involved in work-related nasal symptoms. This study aimed to investigate the contribution of MTHPA exposure to work-related nasal symptoms in a Japanese occupational population.

The mean MTHPA levels in Zone 3 and Zone 4, where the workers were engaged in monitoring operations, were slightly lower than those reported in Sweden (10-85 $\mu g/m^3$) [5]. However, the frequency of positive S-IgE in the workers being currently exposed was 6 of 25 (24%), slightly higher than that in Sweden (18%) [5]. The workers engaged in cleaning the soaking bath, in which a high level of exposure to MTHPA is expected, wore gas masks and rubber gloves for protection from the acetone used in washing. Therefore, the actual level of exposure is considered to be negligible, although confirmation by biological monitoring [9] is needed.

The relationships between S-IgE and nasal symptoms are shown in Table 1. In the IgE-sensitized symptomatic group (SS) and the IgE-nonsensitized nonsymptomatic group (NN), the presence or absence of nasal symptoms agreed completely with the presence or absence of S-IgE. This indicated that there was an IgE-mediated mechanism in at least some of the cases of work-related nasal symptoms associated with MTHPA exposure. Our results are considerably different from those of another study, in which no significant differences were found for ocular and nasal symptoms between IgE-sensitized and unsensitized subjects [3].

This can be partially explained by the fact that our subjects were not exposed to chemicals other than MTHPA, such as the thermal degradation products of plastics [3], which may have irritaing effects on mucous membranes.

Unlike S-IgE, S-IgG4 was not correlated with nasal symptoms in this study. Additionally, Welinder et al. [5] reported that S-IgG4 was significantly associated with the intensity of MTHPA exposure. Further studies are required to clarify the significance of S-IgG4.

The IgE-sensitized nonsymptomatic group (SN) consisted of only one subject. In this worker, we believe that nasal symptoms did not appear because the S-IgE level was very low (0.49 U/ml). This worker might become symptomatic if his S-IgE level increases in the future. The IgE-nonsensitized symptomatic group (NS) consisted of two subjects, one of whom was positive only for S-IgG4. These workers displayed secretion but not the successive sneezing characteristic of allergic rhinitis. The mechanism behind their symptoms remains unclear. Because epoxy resin was the only chemical used in the manufacturing process, their symptoms might have been caused by the irritant effect of MTHPA during the cleaning of the soaking bath. To confirm this, a simple eosinophil test of nasal secretion should be performed [10].

As mentioned, MTHPA is a potent sensitizer that induces S-IgE production and causes nasal symptoms even at very low exposure levels. This indicates that it is difficult to control its effects simply by controlling exposure in the work environment. As shown in Fig. 1, S-IgE has a tendency to be produced as the T-IgE level rises above 80 IU/ml. Therefore, we believe that selection of individuals with a T-IgE level of 80 IU/ml or less, along with improvements in the work environment, is needed to prevent allergic rhinitis caused by MTHPA.

To our knowledge, this is the first study to demonstrate the involvement of MTHPA exposure in work-related nasal symptoms in a Japanese occupational population. Further studies are required to examine the association of S-IgE and work-related nasal symptoms with T-IgE levels in a larger sample of workers.

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