

Study of Employees with Anhydride-Induced Respiratory Disease after Removal from Exposure

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The purpose of this study was to determine the clinical and immunologic status of hexahydrophthalic anhydride (HHPA)-exposed employees who had developed an immunologic respiratory disease and who have been removed from exposure for at least 1 year. In a surveillance study spanning 4 years, we identified 28 employees with HHPA-induced immunologic respiratory disease who had been removed from exposure for at least 1 year. Seven had asthma, nine had hemorrhagic rhinitis, four had both, and eight had allergic rhinitis alone. Respiratory symptoms were assessed by physician-administered questionnaires. For each employee, a physical examination, spirometry, and chest roentgenograph were performed. Antibody against HHPA conjugated to human serum albumin (HHP-HSA) was measured using an enzyme-linked immunosorbent assay. Symptoms, signs, and spirometry normalized in all but one employee. There were no chest-roentgenograph findings at follow-up that could be attributed to HHPA. There was a decline in antibody titer for both immunoglobulin E and G against HHP-HSA. In this group of 28 employees, there was only one employee with mild asthma after removal from exposure for at least 1 year. Although specific antibody was still present in many, the titers were generally lower at follow-up than at presentation.

The acid anhydrides are a well-recognized cause of occupational asthma and other occupational immunologic respiratory diseases.¹ Trimellitic anhydride and phthalic anhydride were among the first reported sensitizing anhydrides. Subsequently, other anhydrides, including maleic anhydride² and methyltetrahydrophthalic anhydride,³ have been reported to cause immunologic sensitization and occupational asthma.

Prevention of occupational immunologic respiratory diseases such as asthma is obviously an important goal.⁴ At the present time, primary prevention through limiting exposure is not possible. In the hope that there would be risk factors that could predict highly susceptible individuals, a number of epidemiologic investigations have been performed. There have been several studies of smoking and atopy as possible risk factors for developing anhydride asthma.^{5,6} In considering the studies as a whole, neither is a strong risk factor. Exposure level appears to modulate the risk of developing anhydride asthma.^{7,8} Preliminary genetic studies suggest that certain human leukocyte antigen haplotypes may predispose to the development of sensitization and occupational asthma in employees exposed to low molecular weight agents such as anhydrides and isocyanates.^{9,10}

In the absence of primary prevention or strongly predictive risk factors, surveillance studies and early removal of affected employees is the

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most common preventive strategy utilized. It is generally accepted that early identification of occupational asthma and removal from exposure will result in a good outcome, provided that the employee has had symptoms less than 1 year and has relatively normal pulmonary functions.⁶ Several studies have reported that removal of workers from the sensitizing agent will result in less airway inflammation on bronchial biopsy.^{11,12} Presumably, this accounts for the abatement of symptoms with removal from exposure. We have previously studied 16 employees with hexahydrophthalic anhydride (HHPA)-induced respiratory disease after they had been removed from exposure for at least 1 year.¹³ All employees were asymptomatic at follow-up.

The purpose of the study presented here was to determine the clinical and immunologic status of employees who had developed an immunologic respiratory disease during our 4-year surveillance study. In all, there were 28 employees who developed an immunologic respiratory disease and had at least 1 year of follow-up after removal from exposure.

Methods

Study Population

The study population consisted of 28 employees at a facility that uses HHPA to prepare a product that contains an epoxy resin. An immunologic respiratory disease caused by HHPA had been diagnosed in each employee: asthma (A), hemorrhagic rhinitis (HR), both A and HR (B), or allergic rhinitis (AR). Criteria for these diagnoses are detailed elsewhere.¹⁴ Each employee had been removed from exposure for at least 1 year.

Exposure Classification

A senior management chemical engineer assigned exposure classifications to each employee in the study population. The classification was

TABLE 1
Demographic Data on Employees with Immunologic Respiratory Disease Caused by HHPA

Characteristic	Allergic Asthma (n = 7)	Hemorrhagic Rhinitis (n = 9)	Both Allergic Asthma and Hemorrhagic Rhinitis (n = 4)	Allergic Rhinitis Only (n = 8)
Age (years)				
Median	37	32	42	33
Range	24 to 41	26 to 45	29 to 63	23 to 55
Sex (F/M)	0/7	0/9	0/4	1/7
Smoking (C/E/N*)	1/2/4	3/1/5	4/0/0	2/0/6
Exposure Category				
1 or 2	2	0	0	2
3 or 4	2	5	3	3
5 or 6	3	3	1	3

* C, current smoker; E, exsmoker; N, never smoked.

based on job description and associated industrial hygiene data, which included air sampling at various workstations in each stage of production of the epoxy-resin product. The classification ranged from 1 to 6, with 1 being the lowest exposure and 6 being the highest exposure. The exposure classification was assigned before determination of whether exposed employees had immunologically mediated respiratory disease as a result of HHPA.

Clinical Evaluation

As in our previous studies, a physician administered a questionnaire to each employee.¹⁵ At the time of the questionnaire administration, neither the physician nor the employee was aware of the results of the most current serologic studies. The questionnaire was developed to assess the type and severity of the employee's symptomatology at the time of diagnosis and at the time of follow-up after at least 1 year of removal from exposure. Physical examination was also conducted at those times. Spirometry and chest roentgenographs were also performed.

Immunologic Studies

During this 4-year surveillance study, immunologic assays were performed with the same methodology. Blood was drawn from each em-

ployee to evaluate immunoglobulin (Ig) E and IgG antibodies against HHPA conjugated to human serum albumin (HHP-HSA). The immunologic assays were performed by enzyme-linked immunosorbent assay analogous to that previously reported for antibody against TM-HSA.¹⁴ To standardize the assay, positive and negative control sera were run with test samples in each assay. The reported serum titer is the lowest dilution of test serum that is greater than twice the optical density of the mean of negative control sera. The serum dilutions used for IgG are 1:10, 1:100, and 1:1000, whereas the IgE serum dilutions are 1:5, 1:10, and 1:50.

Antibody titers were assigned coded scores and chi-squared analyses were performed using SPSS for Windows (Norusis SPSS Inc., Chicago, IL) on a personal computer.

Results

The demographic data on the employees are listed in Table 1. Based on criteria listed elsewhere,^{13,14} there were seven employees with A, nine with HR, four with B, and eight with AR only. No employee had a clear history of hypersensitivity pneumonitis. The employees were generally in the higher exposure categories at the time of diagnosis.

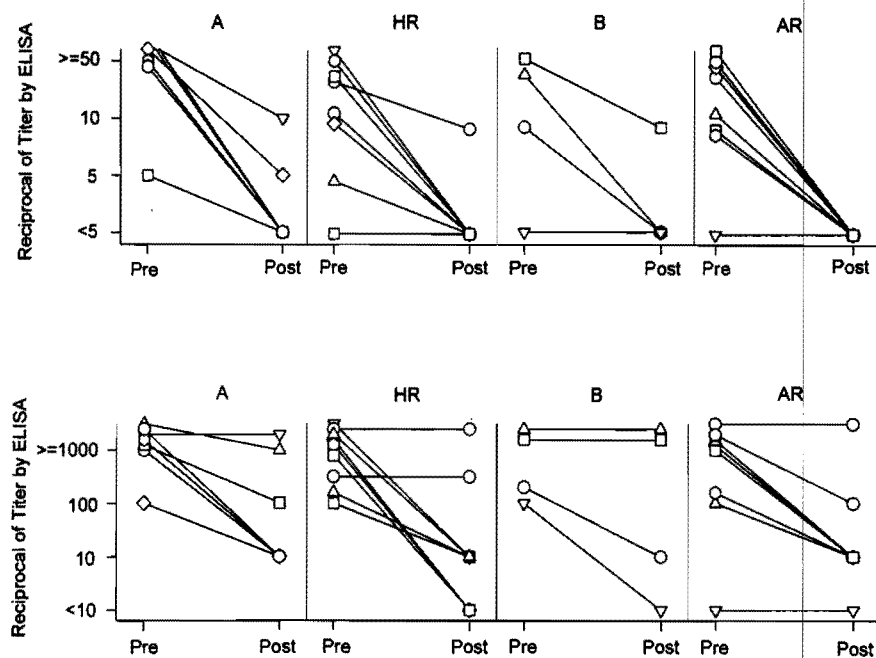


Fig. 1. Titers of specific immunoglobulin (Ig) E (Fig. 1A) and IgG (Fig. 1B) against antibody against HHPA conjugated to human serum albumin (HHP-HSA) before and at least 1 year after removal from exposure in employees with asthma (A), hemorrhagic rhinitis (HR), both (B), or allergic rhinitis only (AR). For illustrative purposes, the individual data points that would be clustered at each titer have been separated to show each individual data point.

Clinical Evaluation

At the time of presentation, all employees had signs and symptoms of A, HR, or AR, but at the time of follow-up there was only one symptomatic employee. He stated that he had shortness of breath and occasional wheezing. His spirometry was normal. His chest exam was normal. His physician had prescribed inhaled albuterol (180 μ g four times daily) and inhaled ipratropium bromide (36 μ g four times daily). Spirometry, which demonstrated mild obstruction (one-second forced expiratory volume, 70 to 80% predicted) in six employees at the time of initial diagnosis, was normal in all employees at follow-up. Chest roentgenographs were normal or abnormalities were unrelated to HHPA exposure in this employee population at both diagnosis and follow-up.

Immunologic Studies

With transfer to jobs devoid of HHPA exposure, the levels of antibody declined in these employees (Fig. 1, A and B). Twenty-five of 28

employees had a decline in titer of IgE against HHP-HSA. The three employees whose IgE did not decline had a titer of $< 1:5$ at diagnosis and follow-up. Twenty of 28 employees had a decline in titer of IgG against HHP-HSA. The eight employees whose IgG did not decline had the same titer at diagnosis and follow-up. No employee had a rise in antibody titer at follow-up.

Chi-squared contingency analyses were performed for both IgE and IgG titers for a relationship between the amount of change in the coded scores before and after removal from exposure. These analyses were not statistically significant (both $P > 0.05$). The finding that is of primary clinical significance, however, is that after removal from exposure, most of the employees had lower titers and none had increased titers for both IgE and IgG antibodies.

Discussion

It is only within the past decade that it has been appreciated that occupational asthma could lead to per-

manent asthma.¹⁶ It was previously believed that removal from exposure to the occupational sensitizing agent would result in cessation of asthma. Studies of employees with asthma resulting from western red cedar¹⁷ and colophony¹⁸ were among the first to report persistence of asthmatic symptoms in those who had been removed for months and even years. Subsequent studies have reported immunologic results in addition to symptomatology and pulmonary function data. In studies of snow crab workers, improvement in lung function and bronchial hyperreactivity, as well as reduction in IgE antibody against a protein antigen, have been reported.¹⁹ With removal from exposure to a low molecular weight antigen (tetrachlorophthalic anhydride), reduction in IgE antibody has also been reported.²⁰ Finally, with transfer of employees to jobs with lower exposure to an occupational sensitizer (trimellitic anhydride), reduction in antibody and some symptom and pulmonary function improvement have been reported.²¹

There is a paucity of long-term follow-up studies of employees with allergic rhinitis or hemorrhagic rhinitis resulting from occupational sensitizers.¹³ In this study, none of the 13 individuals with HR nor any of the eight with AR had symptoms or physical findings of their original diagnosis at their follow-up evaluation. Of the 11 employees with asthma, only one was on medication for mild asthma and no employee had spirometry consistent with asthma at follow-up. In studies of employees with occupational asthma, persistence of symptoms is most likely to occur if individuals have asthmatic symptoms for more than 1 year and abnormal spirometry and bronchial hyperreactivity at time of removal from exposure.⁶ In this surveillance study, only approximately half had mildly abnormal spirometry and only one employee had symptoms for more than 1 year. This is probably why disappearance of

asthma occurred in the great majority.

The uniform decline in IgE antibody in any employee with IgE antibody at time of diagnosis is consistent with immunologic results reported by other investigators.^{19,20} Although IgE did not decline uniformly, it did decrease in most employees after removal from exposure.

In summary, in this employee population of 28 with immunologically mediated respiratory disease as a result of HHPA, there was only one individual with symptomatology despite removal from exposure for at least 1 year. In terms of physical examination, chest roentgenograph, and spirometry, there were no employees with permanent sequelae attributable to HHPA exposure. In all individuals with IgE antibody and in most with IgG antibody, there was a decline in antibody titer at follow-up.

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Historical Bias

Disagreeing with a statement made by then Prime Minister Stanley Baldwin, Winston Churchill declared emphatically: "History will say that the Right Honourable gentleman was wrong in this matter." After a brief pause, he added, "I know it will, because I shall write the history."

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