

A cross-sectional survey of sensitization to *Aspergillus oryzae*-derived lactase in pharmaceutical workers

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Background: The presence of IgE-mediated occupational respiratory sensitization to microbial enzymes has been well documented in a variety of industries. *Aspergillus oryzae*-derived lactase is used as a dietary aid for patients with lactose intolerance. **Objective:** In 1993, a cross-sectional survey of 94 pharmaceutical workers exposed to lactase for a mean duration of 23 months and 24 nonexposed recently hired employees was initiated to identify lactase-sensitized workers and potential risk factors that could be used in making recommendations for preventing future cases of lactase sensitization.

Methods: The survey included a physician-administered questionnaire, skin prick testing to lactase enzyme and a panel of common aeroallergens, and spirometry.

Results: Twenty-seven of 94 lactase-exposed workers (29%) had positive skin test responses to lactase. These workers were 9 times more likely to have upper or lower respiratory symptoms compared with workers with negative skin test responses. Atopic workers were 4 times more likely to have lactase skin sensitivity than nonatopic workers. However, atopy was not a risk factor for the development of upper and/or lower respiratory symptoms. Lactase skin reactivity was not observed in the 24 nonexposed employees.

Conclusion: This cross-sectional survey revealed that atopic workers were more likely to have lactase sensitization and that lactase-sensitized workers were more likely to have upper and/or lower respiratory symptoms, but atopy was not a risk factor for upper or lower respiratory symptoms. In spite of these findings, the company allowed only nonatopic, nonlactase-sensitized workers to continue working in high lactase-exposure areas with careful symptom monitoring and use of protective clothing. Although this strategy was successful in total prevention of new cases of occupational respiratory disease after 5 years, the results of this cross-sectional survey do not support exclusion of atopic workers from working with industrial enzymes. (*J Allergy Clin Immunol* 1999;103:1153-7.)

Key words: Lactase, *Aspergillus oryzae*, sensitization, cross-sectional survey, occupational, respiratory symptoms, pharmaceutical industry, risk factors, atopy

Enzymes are highly sensitizing occupational allergens used in a wide variety of industrial processes. Microbial enzymes are known to cause IgE-mediated occupational asthma and rhinitis.¹ Lactase, a disaccharidase enzyme produced by *Aspergillus oryzae* and *A niger*, is used extensively in the food and drug industries.²⁻⁴ Workers are exposed to lactase in the processing of cheeses and other dairy products.¹ Bakers use lactase as a dough conditioner.⁵ Pharmaceutical workers are exposed to lactase during the manufacturing of digestive aid products for individuals with lactose intolerance.^{1,2} A recent cross-sectional study by Muir et al⁶ reported lactase-induced respiratory symptoms among exposed workers. Lactase-induced symptoms resolved when interventions designed to eliminate lactase dust from the workplace environment were implemented.⁶

In 1993, after a few individuals reported work-related symptoms, our group performed an occupational survey in a population of individuals who worked in a pharmaceutical plant in which lactase digestive aid tablets were manufactured. The source of the lactase or β -d-galactoside galactohydrolase was *A oryzae*. In this article we report results of an initial cross-sectional cohort study performed in a group of lactase-exposed and nonexposed workers to determine the prevalence of IgE-mediated skin sensitization to *A oryzae*-derived lactase. Clinical symptoms and possible risk factors associated with lactase skin sensitization were also evaluated.

METHODS

Work process

The work process involved a series of steps that were performed in separate rooms of the pharmaceutical facility, all under negative pressure. Raw lactase was initially weighed in designated weighing rooms and then dispensed to the blending room where it was sucked up into blenders and mixed with other inert excipients. These 2 areas generated the greatest amounts of lactase dust because they were open systems to the surrounding air. The lactase mixture was transported in open vats to the tableting room where it was compressed into tablets. The compressor machines generated a significant amount of ambient dust air during this process. Coated lactase tablets were packaged into rolls in the autoroll room, and uncoated chewable lactase tablets were packaged in other designated packaging areas. Some of the finished product was then transported to the quality control room for inspection. Workers had direct and uncontrolled exposure to lactase enzymes and tablet dust in all of these

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TABLE I. Defining criteria for questionnaire diagnoses*

Occupational asthma	Two of 3 lower respiratory symptoms (cough, wheeze, or dyspnea), which improve on weekends and/or on vacations
Nonoccupational asthma	Two of 3 of these symptoms, which do not improve on weekends and/or vacations
Occupational rhinitis	One of 3 upper respiratory symptoms (rhinorrhea, nasal congestion, or sneezing), which improve on weekends and/or vacations
Nonoccupational rhinitis	One of 3 upper respiratory symptoms, which do not improve on weekends and/or vacations or actually worsen during pollination season

*Diagnostic criteria are based on standard definitions used in previous cross-sectional occupational surveys. The questionnaire used for this study has been validated for occupational asthma and rhinitis from previous cross-sectional studies in which good agreement was demonstrated between physician diagnosis and serial peak flow studies.^{8,14}

areas. Ambient air measurements of lactase enzyme dust in these processing areas, measured bimonthly with high-volume automated air samplers, ranged from 0.03 mg/m³ to 0.3 mg/m³.

Study population

From a potential group of 250 workers involved in the production of lactase, 118 volunteered to participate in the medical survey. Of these workers, 94 had prior lactase exposure, which ranged from 1 to 44 months, with a mean duration of exposure of 23 months, whereas 24 recently hired employees had no prior history of occupational exposure to lactase at the time of this survey.

Preparation of the lactase skin test reagent

Five grams of lactase supplied by the pharmaceutical company were dissolved in 50 mL of PBS (pH 7.4) overnight at 4°C to yield a 100 mg/mL solution (1:10 wt/vol).⁷ The solution was filtered and dialyzed in PBS for 24 hours. The dialysate was sterilized with a 0.22-μm Millipore filter (Millipore Corp, Bedford, Mass). The final protein concentration was determined to be 30 mg/mL by both the Lowry and Bio-Rad protein assays. Tenfold dilutions of the starting solution were freshly prepared on the test day with sterile PBS. The testing concentrations of lactase reagent ranged from 0.3 μg protein/mL to 30,000 μg protein/mL. No percutaneous irritant responses were observed with these skin test concentrations in 10 nonsensitized volunteers with no known exposure to lactase.

Study design

Each worker signed an informed consent document approved by the New England Investigational Review Board. The itemized questionnaire used in this study had been validated for evaluation of occupational asthma in our previous studies of occupational asthma.⁸ All questionnaires were administered by physicians. The questionnaire captured data pertaining to possible allergic cutaneous or respiratory symptoms at work. Workers were assigned to 1 of 5 symptom categories on the basis of their answers to the occupational questionnaire: category 1, no symptoms; category 2, occupational asthma symptoms; category 3, nonoccupational asthma symptoms; category 4, occupational rhinitis symptoms; and category 5, nonoccupational rhinitis. Predetermined criteria for these diagnoses are summarized in Table I. Other data captured by the questionnaire included the workers' histories of smoking, previous expo-

TABLE II. Characteristics of group 1 workers (n = 94)

Questionnaire diagnoses	Lactase sensitized*	Atopic*	Smoking history*
Normal (n = 72)	0	19 (n = 18)	24.5 (n = 23)
Occupational asthma (n = 7) [†]	6.4 (n = 6)	5.3 (n = 5)	4.3 (n = 4)
Occupational rhinitis (n = 9) [†]	7.4 (n = 7)	4.3 (n = 4)	4.3 (n = 4)
Nonoccupational respiratory symptoms (asthma, bronchitis, or rhinitis) (n = 11)	8.5 (n = 8)	6.4 (n = 6)	3.2 (n = 3)

*Data expressed as percentages of total lactase-exposed workforce (n = 94).

[†]Five workers had both occupational rhinitis and asthma, and 2 workers had diagnoses of both nonoccupational rhinitis and asthma.

sure to lactase, duration of lactase exposure, atopic status, and previous employment.

Prick testing was performed in duplicate sites of the volar aspects of the forearms by using 0.05 mL of the lactase reagent beginning at a concentration of 0.03 μg protein/mL and increasing by 10-fold concentrations every 10 minutes until a positive wheal and flare reaction appeared or the maximum concentration of 30,000 μg protein/mL was attained. A positive reaction to lactase was defined as a wheal greater than 3 mm in diameter with erythema compared to control diluent. Workers also underwent skin prick testing to a panel of 7 common seasonal and perennial aeroallergens, which included dust mite, cat, short ragweed, box elder, *Alternaria* spp, *Cladosporium* spp, and bluegrass. Workers were defined as atopic if they manifested a significant cutaneous reaction (3 mm wheal and erythema larger than that produced by diluent control) to 1 or more of these allergens. Finally, all workers received spirometry, which included forced vital capacity, FEV₁, and FEF₂₅₋₇₅ measurements.

Data analysis

Variables that were analyzed as categorical data included the following: questionnaire diagnoses, presence or absence of percutaneous reactivity to common aeroallergens and the lactase allergen, duration of lactase exposure, and smoking status. These parameters were analyzed by chi-square analysis or with Fisher's exact test, which takes into account small subject groups. Odds ratios and predictive values were used to assess the value of lactase skin testing in this population.

RESULTS

In this cross-sectional study, a total of 118 workers were evaluated, including 94 lactase-exposed (group 1) and 24 recently hired employees never exposed to lactase in a work setting or by personal use as a digestive aid (group 2). Thirty-one workers had been experiencing symptoms at the time of the initial evaluation. Three exposed workers, who had previously ingested lactase digestive aids for prevention of lactose intolerance, were asymptomatic. Table II summarizes the questionnaire diagnoses of group 1 subjects (as defined in Table I) with respect to lactase skin sensitivity, atopy, and smoking status. Seven (7.4%) and 9 (9.6%) of the lactase-exposed workers in group 1 had symptoms consistent with occu-

TABLE III. The relationship between lactase skin prick test reactivity status and respiratory symptoms in lactase-exposed subjects (group 1, n = 94)

Diagnosis	Lactase sensitivity		χ^2	P value	OR*	Sens/Spec†	± value‡
	+	–					
Occupational asthma							
+	6	1	9.18	.002	18.86	0.86/0.76	0.22/0.99
–	21	66					
Occupational rhinitis							
+	7	2	9.19	.002	11.38	0.78/0.76	0.26/0.97
–	20	65					
Occupational respiratory symptoms§							
+	8	3	9.47	.002	8.98	0.73/0.77	0.30/0.96
–	19	64					

*Odds ratios (OR) refer to the likelihood lactase-sensitized subjects will have occupational symptoms compared with nonsensitized subjects.

†Sensitivity (Sens) and specificity (Spec) of lactase skin test.

‡Positive and negative predictive value of lactase skin test for occupational symptoms.

§Occupational respiratory symptoms include asthma and rhinitis. Five workers had both occupational rhinitis and asthma. Two workers with negative lactase skin test responses were assigned a diagnosis of occupational rhinitis, and 1 was assigned a diagnosis of occupational asthma.

TABLE IV. Association of atopy with lactase skin sensitization and occupational respiratory symptoms (group 1; n = 94)

Diagnosis	Atopy		χ^2	P value	OR*
	+	–			
Lactase sensitization†					
+	19	8	6.47	.01	3.75
–	26	41			
Occupational respiratory symptoms‡					
+	6	5	0.02	.88	1.35
–	39	44			
Occupational asthma symptoms					
+	5	2	0.82	.37	2.93
–	40	47			
Occupational rhinitis symptoms					
+	4	5	0.02	.89	0.86
–	41	44			

*Bold values denote significant P value ($P < .05$).

†Odds ratios (OR) refer to likelihood of atopic subjects becoming sensitized to lactase or having occupational symptoms compared with nonatopic subjects.

‡Includes occupational asthma and rhinitis symptoms.

pational asthma or occupational rhinitis, respectively. In group 1, 5 workers had coexisting diagnoses of occupational rhinitis and asthma (5.3%), whereas 2 workers had both nonoccupational rhinitis and asthma (2%). Among the group 2 employees, 2 were assigned diagnoses of nonoccupational rhinitis, and 1 was assigned a diagnosis of nonoccupational asthma.

Questionnaire diagnoses and skin test reactivity to common aeroallergens and the lactase reagent are summarized in Table II. Twenty-seven (29%) of the 94 lactase-exposed workers had positive skin prick test responses to the lactase antigen. Of these, 19 (20%) were atopic (skin reactivity to at least 1 aeroallergen). Endpoint skin test threshold concentrations were evenly distributed among the lactase skin-sensitized workers: 3 reacted at 0.03 $\mu\text{g/mL}$; 3 at 3 $\mu\text{g/mL}$; 6 at 30 $\mu\text{g/mL}$; 7 at 300 $\mu\text{g/mL}$; 6 at 3000 $\mu\text{g/mL}$, and 2 at 30,000 $\mu\text{g protein/mL}$. None of the nonexposed (group 2) workers demonstrated percutaneous reactivity to the lactase reagent.

The average duration of lactase exposure in group 1 workers before evaluation was similar among all diagnostic categories. The duration of lactase exposure in clinically symptomatic workers ranged from 1 to 44 months, with a mean duration of 23 months. In nonatopic workers the mean duration of exposure to lactase was 7 months longer than that found in atopic coworkers.

Table III summarizes analyses of associations of percutaneous sensitivity to lactase and occupational respiratory diagnoses derived from questionnaires. Lactase skin testing was moderately sensitive and specific for identifying workers with either occupational asthma or occupational rhinitis. A negative lactase skin prick test response had excellent negative predictive value for identification of workers without occupational symptoms. Significant associations were found between lactase skin prick test sensitivity and the diagnoses of occupational asthma alone, occupational rhinitis alone, and combined

occupational asthma and rhinitis ($P < .002$). A lactase-sensitized worker was 9 times more likely to have occupational respiratory symptoms compared with a nonlactase-sensitized worker (Table III).

A significant association was also found between atopy and lactase skin prick test reactivity (Table IV; $P < .011$). Nineteen atopic subjects demonstrated lactase skin sensitivity compared with 8 nonatopic individuals. Atopic workers were nearly 4 times more likely to have percutaneous reactivity to lactase compared with nonatopic workers, suggesting that atopy was a risk factor for lactase skin sensitization (Table IV). However, atopy itself was not associated with occupational asthma or rhinitis (Table IV).

Although not statistically significant, a trend toward shorter duration of exposure was observed in atopic workers in whom lactase skin sensitization developed compared with nonatopic workers. Four atopic workers had skin sensitivity to lactase within 6 months of their initial lactase exposure, whereas none of the nonatopic workers exhibited lactase skin sensitization unless they had been exposed for at least 6 months. Significant associations were not demonstrated between lactase skin sensitization and smoking or between smoking status and occupational respiratory symptoms (data not shown).

On the basis of pragmatic concerns of the company to exclude all possibility of clinical sensitivity in a newly engineered plant, all new workers were screened for atopy and lactase sensitization. Only nonatopic workers were permitted to work in high lactase exposure areas. This intervention was based partially on the cross-sectional data, which demonstrated an increased association between atopy and lactase sensitization, but more so because of the company's administrative directive. Air supplying body suits and respirators were also recommended as additional protective measures. After completion of the cross-sectional study, the production facility was redesigned to ensure that lactase air levels did not exceed 0.0001 mg/m^3 ($0.1 \text{ } \mu\text{g/m}^3$). Serial ambient air sampling in areas where workers were not required to wear protective garments or respirators was monitored to ensure that lactase exposure levels remained below $0.1 \text{ } \mu\text{g/m}^3$. The ambient level of lactase dust in the high exposure areas where protective garments were required ranged from 2.0 to $10 \text{ } \mu\text{g/m}^3$. This combined approach was completely effective in preventing respiratory symptoms in the 11 workers who were monitored biannually with spirometry for 5 years (1993 to 1997) and lactase skin testing through 1994 in the new facility.⁹

DISCUSSION

In this report a group of pharmaceutical workers in whom respiratory symptoms developed after a mean period of exposure of 23 months to *A oryzae*-derived lactase were evaluated. The objectives of this study were to determine whether IgE-mediated skin sensitization to lactase had developed in lactase-exposed workers, to define clinical symptoms associated with lactase skin

sensitization, to identify possible risk factors associated with lactase skin sensitization, and to make recommendations for prevention of new cases in exposed workers.

Atopy was a risk factor for lactase skin sensitization, but not for occupational asthma or rhinitis symptoms, a result which is supported by similar findings in previous studies.¹⁰ Muir et al⁶ also reported that atopic workers exposed to lactase were more likely to become skin sensitized. Their results differed in that positive skin test responses to lactase correlated with symptoms of rhinitis and conjunctivitis, but not with asthma. Absence of this association could be explained by reliance on questionnaire-derived data, which are known to have limited diagnostic specificity.

In this study, although a positive lactase skin test response was a relatively poor positive predictor for symptomatic status, a negative skin test response demonstrated excellent predictive value for excluding symptomatic status in workers ($>95\%$). Both sensitivity and specificity of the lactase skin test were moderately good in this analysis (Table III). The absence of an irritant lactase skin test response in our normal control subjects and in the asymptomatic, lactase-exposed workers with negative skin test responses at relatively high concentrations ($30,000 \text{ } \mu\text{g/mL}$) is in contrast to findings in previous similar studies that used threshold skin testing methods to evaluate skin sensitization of proteolytic enzymes.^{11,12} This observation is likely a reflection of the less irritating nature of disaccharidase enzymes (ie, lactase) compared with proteolytic enzymes (ie, papain and other *Bacillus subtilis*-derived enzymes).^{11,12}

Duration of exposure and smoking status were not found to be significant risk factors for lactase sensitization. Similarly, a previous study was unable to demonstrate a significant correlation between the estimated level of exposure and lactase sensitization.⁶ However, smoking status appears to be a risk factor for sensitization to other natural protein workplace allergens, such as snow crab or laboratory animal proteins.^{13,14}

It is important to note that oral ingestion of the lactase product did not appear to be associated with either lactase skin sensitization or symptomatic status. Three lactase-exposed workers who had previously used the lactase supplement had negative lactase skin test responses and were asymptomatic. Furthermore, there have been no reports from consumers to the pharmaceutical company regarding an increase in respiratory symptoms after ingestion of this lactase supplement. This is consistent with previous experience in egg-processing workers who had IgE-mediated occupational asthma associated with inhalational exposure to egg proteins but rarely reported reactions after ingestion of eggs.^{15,16}

Although this study did not identify atopy as a risk factor for lactase-induced occupational asthma or rhinitis, the company chose a conservative approach to prevent the possibility of any future cases of lactase-induced sensitization or respiratory symptoms. They only allowed workers with normal pulmonary function ($\text{FEV}_1 \geq 80\%$) and negative skin test responses to common

aeroallergens and lactase to work in a new lactase-producing facility specifically designed to reduce lactase exposure. These workers were required to wear an air supplying total body suit while working with lactase, and they were also required to shower after each work shift. The health care personnel at the pharmaceutical plant were trained to perform lactase skin testing at 6-month intervals on all exposed workers. All of the workers who continued to be exposed to lactase continued to have negative lactase skin test responses and to be asymptomatic through 1994.⁹ After 5 years of total barrier exposure conditions, no new cases of occupational asthma or rhinitis symptoms were observed in the 11 workers in work areas with lactase concentrations of at least 2 µg/m³.⁹ Lactase skin testing in these 11 workers from 1994 through 1997 was not performed.⁹ Follow-up lactase skin testing in the original 27 workers shown to have positive lactase skin test responses during the original cross-sectional study was not performed either because of loss of follow-up after reassignment to other jobs within the company or termination of employment from the company.

Recommendations to exclude atopic workers from further lactase exposure was the decision of the company as an extra precaution to prevent any future cases of lactase sensitization and/or subsequent occupational respiratory symptoms. However, it should be emphasized that atopy itself was not a risk factor for future respiratory symptoms in this study, and therefore such a strategy is not applicable to enzyme-exposed workers in other industries.

In summary, the results of this study further support previous evidence that enzymes are highly sensitizing proteins that can induce sensitization. Because these proteins have been used increasingly in a variety of industries, reports of occupational respiratory disease have dramatically increased.¹⁷⁻¹⁹ Attempts to modify enzyme exposure by making individual particles less respirable have been helpful but not entirely successful in eliminating the risk for sensitization in susceptible individuals.²⁰ Therefore it is essential that surveillance of both atopic and nonatopic workers, along with continuous ambient air monitoring programs, be established in plants where these allergenic materials are used to prevent clinical sensitization.

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