Isolated Late Asthmatic Reaction After Exposure to a High-Molecular-Weight Occupational Agent, Subtilisin*

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High-molecular-weight agents generally induce immediate asthmatic reactions. We report the case of a subject who experienced a reaction that started after the first hour following exposure to subtilisin, a high-molecular-weight occupational agent. Any occurrence of immediate reaction was ruled out by measuring both FEV₁ and lung volumes every 10 min in the first hour. This reaction was IgE-mediated as shown by immediate skin reactivity and increased specific IgE levels.

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Key words: asthma; occupational lung disease

Abbreviations: PC₂₀ = provocative concentration causing a 20% fall in FEV₁; SIC = specific inhalation challenge

Case Report

A 41-year-old subject had been working since 1991 in a surgical department. He had had no history of asthma but had complained of hay fever since 1992. He had smoked 10 pack-years. His work consisted of washing surgical tools with a liquid (Klenzyme) containing a proteolytic enzyme, subtilisin. One year after beginning this work, he developed cough and eye itching at work. His symptoms progressively worsened and he experienced cough at work, as well as cough, dyspnea, and wheezing at the end of work days, with nocturnal symptoms also. He was asymptomatic during weekends and on holidays. He had been investigated in February 1993, at which time he underwent a nonspecific inhalation challenge test to methacholine. The provocative concentration causing a 20% fall in FEV₁ (PC₂₀) was 0.06 mg/mL, reflecting severe bronchial hyperresponsiveness. 1 Monitoring of FEV₁ at work then showed a decrease in FEV₁ from 3.25 L (predicted: 3.93 L, 82.7% predicted) at 10:15 AM, to 2.62 L (66.6% predicted) at 3:45 PM.

Skin tests performed by the prick method with common inhaled and occupational agents showed immediate weal reactions to tree and grass pollens and Aspergillus fumigatus. Prick tests performed with pure diluted subtilisin (1 mg/mL, 1 mg/10 mL, 1 mg/100 mL) showed immediate weal diameters of 9 mm, 8 mm, and 5 mm, respectively.

Specific IgE antibodies were measured with a subtilisin radioallergosorbent test and expressed as a percent of bound IgE. The serum samples of six nonatopic subjects served as controls. Their mean ± SD specific IgE value was 4.4 ± 0.6%. Any value greater than 5.7% (upper limit of 2 SD of the mean) was considered to reflect significantly increased specific IgE values. Our subject's result was 31.7% bound.

Specific inhalation challenges (SIC) were performed in May 1995, at a time when the subject had not been exposed at work for 1 month. Baseline FEV₁ was 3.65 L (93% predicted), and FVC was 4.71 L (102% predicted). PC₂₀ was 6.8 mg/mL (mild bronchial hyperresponsiveness). Thirty minutes of exposure to the vapor of a paint thinner (Varsol) on the control day did not cause any significant change in FEV₁ (Fig 1). On the next day, we exposed the subject to the diluted liquid surgical cleanser (Klenzyme) (25 mL in 4 L of water for the first 30 min, then, 75 mL in 4 L of water for the subsequent 40 min), asking him to breathe the vapor of this liquid in a cubicle in a progressive fashion for a total of 70 min. Four hours after the end of exposure, the subject experienced a late asthmatic reaction (25% fall of FEV₁) (not illustrated). This unexpected result led us to carry on the following investigation. We again exposed the subject to diluted liquid surgical cleanser (Klenzyme) (75 mL into 4 L of water) in a progressive fashion for a 50-min interval. We monitored lung volumes before exposure, 30 min after, and then, hourly until an asthmatic reaction occurred. We expected that monitoring of lung volumes would allow us to detect a possi-
Occasionally hidden immediate asthmatic reaction, one that could be revealed by hyperinflation only. Our subject experienced a late asthmatic reaction that was maximal 210 min after the end of exposure (23% fall in FEV1) (Fig 1). Residual volume increased from 1.86 L (94% predicted) before exposure to 2.63 L (133% predicted) 4 h after exposure, but was unchanged during the first hour after exposure (Fig 1). The morning after, PC20 was significantly decreased at 1.4 mg/mL. As we suspected that the lack of immediate asthmatic reaction could be explained by a low release of inflammatory mediators, we performed, all on the same day 4 months later, bronchial challenges to methacholine, histamine, and isocapnic hyperventilation of cold air. The rationale was that histamine and methacholine are stimuli acting directly on smooth muscle, whereas hyperventilation of cold air acts on the same target through local stimulation of cells secreting mediators. PC20 methacholine was 2.9 mg/mL and PC20 histamine was 4 mg/mL, whereas a 20% change in FEV1 could not be reached after ventilating 101 L/min at maximum voluntary ventilation.

**DISCUSSION**

Isolated late asthmatic reactions are uncommon after exposure to high-molecular-weight agents. Among 117 subjects who underwent positive SIC to high-molecular-weight agents in our center in the past 10 years, only 2 experienced early-late reaction after exposure to flour. However, these subjects had, respectively, 8% and 10% falls in FEV1 in the first hour, but lung volumes were not monitored. Some authors have observed isolated late reactions after exposure to common inhalants. Ihre and coworkers reported the occurrence of late asthmatic reactions after SIC to birch pollen and weeping fig in 6 asthmatic subjects among 13 investigated. Lung volumes were not monitored. Four of these six subjects experienced a dual reaction after increasing allergen concentration. The authors hypothesized that when a low-dose allergen does not induce immediate obstruction in central airways, then the allergen is able to reach peripheral airways and give rise to an isolated late reaction with obstruction of the small airways.

The occurrence of an isolated late asthmatic response can be explained by an IgE-mediated mechanism associated with secondary mediators (prostaglandins, platelet-activating factor, or leukotrienes). However, this is usually preceded by an immediate asthmatic reaction. As the reaction induced by cold air was lower than the one induced by methacholine in our subject, it can be hypothesized that our subject’s ability to have an immediate IgE-mediated asthmatic reaction (with release of mast cell mediators) was weak. This may explain why he experienced a late asthmatic reaction only after exposure to a high-molecular-weight agent.

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**REFERENCES**


