Occupational Asthma in Female Factory Worker Resulting from Exposure to Savinase in Dishwashing Tablets—A Case Study

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Abstract: Occupational Asthma in Female Factory Worker Resulting from Exposure to Savinase in Dishwashing Tablets—A Case Study: Agnieszka Lipińska-Ojrzanowska, et al. Department of Occupational Diseases, Nofer Institute of Occupational Medicine, Poland—Objectives: Savinase is one of the endopeptidases widely used in washing detergents. Its ability to cause respiratory allergy has been known. Up to now, most cases of occupational asthma (OA) to savinase have been described among workers involved in the manufacture of laundry detergents. We present a case study of 51-year-old female worker of a dishwashing tablets factory, who had been packaging ready-made tablets into foil wrappers for 4 years and developed respiratory symptoms, such as cough, dyspnoea and wheezing. Methods: A number of clinical procedures were performed, including the clinical examination, routine laboratory tests, evaluation of total and allergen-specific serum IgE (asIgE) to enzymes, skin prick tests for common allergens, rest spirometry, inhalation methacholine challenge test and a single-blind, placebo-controlled specific inhalation challenge test (SICT) with dishwashing tablets. Results: Clinical findings and results of routine laboratory tests were within normal limits. Baseline nonspecific bronchial hyperreactivity was revealed. In patient’s serum blood we found significantly elevated asIgE to savinase. Decline of FEV₁ and PEF in late phase of asthmatic reaction was observed during the specific challenge test. The patient reported chest tightness between 5−12 hours after exposure to dishwashing tablet ingredients. Cytological assessment of an induced sputum revealed increase in the percentage of eosinophils 24 hours after specific challenge in comparison to values noted before the SICT. Conclusions: Positive clinical response to the challenge confirmed in objective method tests validated the diagnosis of OA.


Key words: Detergents, Dishwashing tablet, Occupational asthma (OA), Savinase, Sensitization to enzymes, Subtilisin

In the 1960s, proteolytic enzymes were introduced into detergent laundry products. These subtilisin-like serine proteases are produced by alkalophilic bacteria (Bacillus sp. strain). One of these endopeptidases is savinase, which is extremely useful in biotechnological processes of various industrial fields. It represents a subgroup of high-alkaline proteases belonging to subtilase family enzymes with maximum stability between 7−10 pH and the highest activity in the range of 8−12 pH. The structure of savinase is similar to other homologous Bacillus subtilisins¹,². The most effective hydrolysis of peptide bonds by savinase takes place in the temperature range between 20 and 60°C. Due to these protein-degrading chemical properties, savinase has found practical application in washing powders and dishwashing products designed for removing protein-based stains and residues (food, blood, feces).

In spite of the wide usefulness of subtilisins in detergent production, all of them are high-molecular-weight antigens (HMW), and their ability to cause respiratory allergy among workers involved in the manufacture of laundry detergents has been known³−⁵. Increasing numbers of occupational rhinoconjunctivitis and asthma cases due to proteolytic enzymes have resulted in the necessity to minimize inhalation exposure to them, for example, through improving production space ventilation, encapsulating the process of manufacturing and using personal protec-
tive equipment for workers. Efficient implementation of preventive procedures since the 1970s has resulted in a decreasing trend in the incidence of allergy to proteolytic enzymes. However, incomplete application of preventive measures may result in new cases of occupational sensitization⁷.⁸.

The aim of this paper was to present the clinical case of a worker who developed occupational asthma as a result of sensitization to savinase contained in dishwashing tablets designed for use in automatic dishwashers.

Case Presentation

A 51-year-old woman, who had been working for 4 years as a process operator in a dishwashing tablets factory, developed wheezing, cough and shortness of breath. Packaging ready-made dishwashing tablets in foil wrappers fell within her duties. Before hospitalization in the Department of Occupational Diseases in the Nofer Institute of Occupational Medicine due to suspicion of occupational asthma, the patient had not been working for 6 months based on medical certificate, that indicated incapacity for work caused by chronic infection of the pulmonary tract. On the basis of data obtained from employer and safety data sheets for the dishwashing tablets, we determined the main detergent compounds she was exposed to (sodium carbonate, oxygen-based bleaching agents, proteolytic enzymes, alpha amylase and subtilisins). The content of subtilisins was estimated to be 0.00006 mg/m³, the permissible exposure limit established by the Occupational Safety and Health Administration (OSHA PEL)⁷.⁹.

On admission to our clinic, the patient did not complain about any respiratory ailments. She was informed about the process of planned research in a written manner; hospitalization required written informed consent. A detailed questionnaire focusing on present and past medical history, a physical examination, chest radiography and routine laboratory tests were carried out. Skin prick tests (SPTs) for common allergens including tree and grass pollens, moulds and mites, Dermatophagoides farinae and Dermatophagoides pteronyssinus, were performed on the volar part of the forearm using commercial extracts and standardized disposable lancets (Allergopharma, Germany). All SPTs included positive (10 mg/ml histamine hydrochloride, Stallergenes, France) and negative controls (phenylated glycerol-carbonate, oxygen-based bleaching agents, proteolytic enzymes, alpha amylase and subtilisins) (10 mg/m³). The results were assessed after 15 minutes. The levels of total serum immunoglobulin E (IgE) and allergen-specific IgE antibodies (asIgE) in response to alpha-amylase (k87), maxatase (k204), alkalase (k205) and savinase (k206) (Phadia, Uppsala, Sweden) were evaluated in the patient’s blood. All spirometric measurements, including a methacholine inhalantion challenge test, were carried out by using MasterScope PC spirometer equipment (Jaeger, USA). Then a gold standard-like condition—a single-blind, controlled test with placebo (talcum powder: Mg,H₄Si,O₁₂) work—specific challenge test (SICT) with potential allergens (powder of crushed dishwashing tablets) was performed. The patient sifted each powder for 60 minutes in a cubical chamber (6 m³) with 2 days between the challenge tests. Induced sputum (IS) samples were collected before the provocations as well as 24 hours afterwards. The cellular composition of IS samples was analyzed⁸. During the 24 hours after the start of exposure to specific inhalant agents (talcum and detergents powder), hourly spirometry and peak expiratory flow (PEF) measurements were noted.

Questionnaire-derived data pointed to a clear relation of patient’s respiratory symptoms to work environment. Shortness of breath, wheezing and dry cough exacerbated during 8 hours of shift work and improved while she was away from work (weekends, holidays). The patient denied having a smoking habit and had never been treated for allergies. Family history of atopy was positive: her daughter suffered from atopnic dermatitis. The physical examination and chest X-ray performed on admission to the Department of Occupational Diseases did not reveal any abnormalities. Routine laboratory parameters were within normal limits. The SPTs for common allergens and alpha-amylase were negative. The total IgE level was insignificantly elevated to 116.02 IU/ml. Specific IgE antibodies to alpha-amylase, maxatase and alkalase were not detected, but the level of asIgE to savinase was 3.99 kUA/l. The baseline values of other spirometry tests were normal: forced expiratory volume in one second (FEV1)=2.28 l (90.5% of predictive values), forced vital capacity (FVC)=3.13 l (105.8%), FEV1/FVC ratio=72.89 %.

The baseline methacholine inhalation challenge test revealed nonspecific bronchial hyperreactivity (BHR) (PC₂₀=1.6,6 mg/ml).

The inhalant challenge test with a placebo did not cause any changes. There were no clinical symptoms of bronchial obstruction. We did not observed any significant changes in spirometric and PEF values (Fig. 1) or eosinophils count in an induced sputum sample collected 24 hours after the exposure to talcum powder (Fig. 2). The methacholine inhalation challenge test was interrupted after 30 sec due to the patient’s request because of a feeling of irritation in the throat and intensive cough. It was not continued because the patient declined to continue.

Five hours after SICT with dishwashing tablet powder, the patient reported tightness of the chest.
Vesicular rustle was quieter in comparison to baseline auscultation. We observed a late asthmatic reaction with 27% decrease in FEV$_1$ in the 6th hour of the challenge (Fig. 1). The specificity of the asthmatic reaction was confirmed by a significant increase of eosinophil count in induced sputum samples collected before and after 24 hours of specific inhalation exposure (from 3 to 12%; Fig. 2). BHR could not be assessed because the patient refused to be subjected to the methacholine challenge test.

The diagnosis of occupational asthma was made based on the typical clinical symptoms after exposure to dishwashing detergents confirmed by positive results of objective tests.

**Discussion**

The usefulness of industrial enzymes has increased during the last decades, especially in the detergents production field. Although traditionally used in laundry products, proteases have been successfully incorporated into toothpastes, dishwashing liquids and powders. The first report of asthmatic reaction induced by sensitization to industrial enzymes (alkalase, maxatase) in detergent factory workers was published in 1969\(^3\). After that, a number of epidemiologic industry studies revealed high allergy prevalence among workers occupationally exposed to proteases, which in less than 10 years made it necessary to enact regulations on recommended safety procedures.
Some producers even ceased using enzymes, and some employers began taking up “prophylactic steps” decided to exclude atopic workers from detergents processing. As a consequence of widespread improvement in the industrial hygiene, the problem of enzyme-induced airway sensitization seemed to have disappeared. However, a high prevalence of work-related respiratory symptoms (16%) connected with sensitization to enzymes was reported in a detergent factory in the United Kingdom. Intensive growth of industrial technologies has brought safer methods of detergent production as well as new hazards to health. To our knowledge, the present report is the first case of occupational asthma developed due to exposure to savinase in a dishwashing tablets factory setting; however, the mechanism of the disease seems to be similar to allergic antibody-mediated OA recognized previously among workers involved in laundry detergents production.

The principal limitation of our study is the lack of analysis of the airborne particle distributions in the breathing zone at the workplace. A survey carried out in a modern European detergent factory that used encapsulated enzymes revealed that enzyme sensitization and work-related respiratory symptoms were positively correlated with airborne enzyme exposure, which suggested that encapsulation alone is not sufficient to prevent enzyme-induced airway allergy.

In the present case description, the patient’s respiratory symptoms were predominantly moderate and related to the work environment, so the clinical history visibly suggested occupational airway allergy. However, some epidemiologic studies point to high sensitivity, but not specificity, of questionnaires used as a single tool for detection of occupational asthma.

Sensitization to savinase was shown only by the level of asIgE due to unavailability of standardized enzyme extracts for SPT (except alpha-amylase) during the patient’s hospitalization. The cut-off value for detection of specific IgE was 0.35 kU/l. According to Phadia, the expected test sensitivity was in the range of 84–95% and the specificity was in the range of 85–94%. The significantly increased level of asIgE in response to savinase suggested strong occupational sensitization; however, precipitating antibodies to subtilisins had been found also in unexposed controls.

In conclusion, the specific inhalation challenge test as a gold standard for the diagnosis of occupational allergy demonstrated a certain direct relationship between exposure to dishwashing detergents contained in encapsulated tablets and an asthmatic response.

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**References**