Analysis of the clinical state of patients with occupational asthma following cessation of exposure to allergens

P. Górski, B. Kołacińska and T. Wittczak
Department of Occupational Diseases, Nofer Institute of Occupational Medicine, Łódź, Poland

The purpose of this study was to evaluate the health state of patients with occupational asthma after cessation of occupational exposure to bakery allergens. A follow-up study of 56 subjects with occupational asthma was carried out. Subjects were examined twice: 1–6 months after removal from occupational exposure and 36 or 48 months later. Clinical state analysis both at diagnosis and re-examination was performed with the use of a questionnaire. Functional spirometric tests and skin prick tests and/or specific serum IgE were carried out during both examinations at points of time at which the subjects regarded their asthma symptoms as least severe. According to the subjective evaluation of the patients' clinical state, some improvement could be noticed 36 or 48 months after removal from work. Forced expiratory volume in one second (FEV₁) and peak respiratory flow (PEF) did not change significantly. Total serum IgE concentration decreased in only two subjects, but the mean value of total IgE level did not significantly differ at the first and second examination after the cessation of occupational exposure. There was no significant difference in the number of positive skin prick tests to common and occupational allergens between the first and second examination. The majority of patients with occupational asthma reporting subjectively on their symptoms indicated an improvement in their clinical state 2–3 years after removal from occupational exposure. The intensity of skin prick tests was not reduced in the studied group. Non-specific bronchial hyper-responsiveness was not reduced in the majority of subjects with occupational asthma at least 2 years after cessation of occupational exposure.

Key words: Asthma; cessation of exposure; follow-up study; occupational prognosis.

INTRODUCTION

The natural history of occupational asthma and its clinical course may significantly differ by country since occupational allergens, working conditions and the level of health care vary between different societies. For example, smoking habits may affect the factor of occupational exposure cessation. Prophylactic activities concerning occupational asthma can be influenced by general socio-economic conditions as well. The results of several studies on the course of occupational asthma show that ventilation disorders, airway obstruction, non-specific bronchial hyperactivity (NSBH) and clinical symptoms may persist after the cessation of exposure. However the significant improvement in spirometric parameters and the decrease in non-specific bronchial hyperactivity can be observed not only as the result of treatment with inhaled corticosteroids and other anti-inflammatory drugs but also over the natural course of the disease following exposure cessation. The aim of our study was to investigate how cessation of occupational exposure to allergens influenced the course of occupational asthma in the studied group of patients.

MATERIALS AND METHODS

Subjects

Fifty-six out of 67 subjects with baker's asthma participated in the study. They were examined in the Institute
of Occupational Medicine, a reference institution diagnosing occupational asthma in Poland. The 56 subjects with occupational asthma were clinically observed for the first time 1–6 months after the end of occupational exposure and were re-examined 36 or 48 months later. Throughout this time, the subjects were under the observation and treatment of allergists employed in the Institute of Occupational Medicine. The re-examination, however, was conducted by another allergist — one of the authors of the study.

The age of patients ranged from 20 to 56 years. All subjects participating in the study had been employed in different bakeries working with open production cycles. The study was not performed in 11 of the 67 subjects, because of socio-psychological problems.

The diagnosis of occupational asthma

The following criteria of the diagnosis of occupational asthma were used: positive medical history, relevant exposure assessed in the occupational history analysis and at least one positive allergological examination (skin prick test and/or specific serum IgE level). In 49 cases a significant fall in Peak expiratory flow rate (PEFR) — at least 20% of the initial value at the workplace — was observed. In seven cases PEFR measurements were not performed because of technical problems. All patients were sensitive to flour, 43 were also allergic to house dust mites and 21 to tree or grass pollens.

Analysis of health state

The analysis of clinical status, during both diagnosis and re-examination was based on a questionnaire covering: the intensity of coughing and dyspnoea (shortness of breath); mean daily use of inhaled beta agonists and daily dose of oral and inhaled corticosteroids. The questionnaire was administered by a physician. Analysis were carried out for the month in which the subject was in the best condition in the three months preceding the clinical examination. Each patient evaluated his own physical strain tolerance and the intensity of dyspnoea and coughing on a 0–3 point scale: 0 = lack of symptoms (asymptomatic subjects); 1 = mild dyspnoea; 2 = medium-intensity dyspnoea and 3 = the most severe dyspnoea in the last three months.

The patients recorded their symptoms according to the above scale in the month which they regarded as their period of best condition.

During the first examination 40 patients suffered from moderate asthma and 16 from severe asthma. The severity of the disease was assessed according to the Global Strategy for Asthma Management and Prevention.1

Pulmonary function and histamine challenge testing

The subjects underwent certain functional spirometric tests (using spirometer Victest P2a, Mijnhardt, Holland) in both periods regarded by themselves as clinically optimal. Functional spirometric tests comprised a bronchial reversibility test after application of one puff of inhaled β-agonist (salbutamol 100 μg/puff) with the parallel assessment of the forced expiratory volume in one second (FEV1). The test was regarded as positive with reversibility at least 20% of FEV1. Daily variability of PEFR was observed during at least one week in the ‘best condition month’ preceding the clinical examination. A histamine inhalation test was performed and PC20 was determined. Prior to histamine challenge all the subjects presented with baseline FEV1 above 70% of the forced vital capacity (FVC). Normal saline solution of histamine dihydrochloride obtained from Sigma Chemical Company was prepared directly before the inhalation and delivered through the DeVilbiss nebuliser No 646. The histamine concentrations were as follows: 0.03, 0.06, 0.125, 0.250, 0.5, 1, 2, 4, 8 and 16 mg/ml. Histamine PC20 FEV1 was defined as a provocative concentration of histamine producing a 20% fall in FEV1.

Skin prick tests

Skin prick tests with a battery of the most common allergens (commercial set of Allergopharma, Germany) including dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae); grass pollens (velvet grass, cocksfoot, rye grass, Timothy, blue grass, meadow); tree pollens (alder, hazel, poplar, elm, willow, birch, beech, oak, plane tree); moulds (Alternaria tenuis, Botrytis cinerea, Cladosporium herbarium, Currularia lunata, Fusarium moniliforme, Helminthosporium halodes, Aspergillus fumigatus, Mucor mucedo, Penicillium notatum, Pullularia pullulans, Rhizopus nigricans, Serpula lacrymans); feathers (duck, goose, hen) and flours (barley, oat, corn, rye, wheat) were carried out. The negative control was allergen diluent and the positive was one-histamine solution. All the tested sites were examined after 20 min: wheals of 3 mm > control and flares of 5 mm > control were considered positive.

Serum studies

Serum IgE level was determined using the immunoenzymatic method (enzyme immunoassay, Pharmacia, Sweden). Total IgE level ≥ 100 ku IgE/l was treated as high. Levels of specific IgE antibodies were determined in all patients with negative skin prick tests to occupational allergens by radioallergosorbent test (RAST, Pharmacia, Sweden).

Statistics

All analyses were performed with Microsoft Excel. The means and standard deviations were calculated. The results obtained for the first time after the end of occupational exposure were compared with those obtained 36 or 48 months later using the Student’s t-test. The differences were regarded as significant at p < 0.05.

RESULTS

At the first examination, 15 patients were active smokers, 26 had never smoked and 15 subjects smoked in the past
(ex-smokers). During re-examination 36 or 48 months later it was found that eight subjects were still active smokers, 26 subjects had never smoked and 22 persons were ex-smokers.

None of the subjects followed the principles of allergy prevention to a degree which could have affected clinical status. After diagnosis of occupational asthma, nine subjects changed their jobs and were no longer directly exposed to occupational hazardous irritants or sensitizing agents; the others stopped working completely.

The clinical state of the subjects at first examination differed from that at re-examination carried out 36 or 48 months later. During the first clinical observation, 26 patients reported that during the period of well-being, dyspnoea with a severity of '3' (according to the scale described before) occurred 3-5 times a month and in 30 subjects shortness of breath with a severity of '1' occurred 15 times a month.

Physical strain tolerance was generally subjectively evaluated as 'bad'. Forty-five of the 56 subjects complained of dyspnoea after a few minutes of rapid walking or climbing one flight of stairs. The intensity of coughing was strictly correlated with the occurrence of effort dyspnoea.

According to the subjective evaluation of the subjects clinical state, some improvement could be noticed after 36 or 48 months post-exposure, as dyspnoea assessed as '3' occurred twice a month on average; assessed as '2', about 6 times a month and assessed as '1', eight times a month. Improvement in physical strain tolerance was also observed as all subjects were able to walk quickly or climb three flights of stairs without dyspnoea.

Daily use of beta agonists was reduced in all subjects from 6.47 puffs per day to 4.12 puffs per day on average. The use of oral corticosteroids was also reduced. Thirty-one patients had no need for them and another 23 patients used oral corticosteroids. There was no difference in the number of subjects treated with inhaled corticosteroids; the others stopped completely.

Table 1. Pulmonary function and histamine challenge testing in the group of bakers examined 1-6 and 36-48 months after the end of occupational exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1-6 months (mean ± SD)</th>
<th>36-48 months (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ l/s</td>
<td>3.5 ± 0.5</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>PEFR l/min</td>
<td>23.7 ± 10.5</td>
<td>21.8 ± 13.6</td>
</tr>
<tr>
<td>PC 20 mg/ml</td>
<td>2.76 ± 1.0</td>
<td>2.78 ± 0.8</td>
</tr>
<tr>
<td>p &gt; 0.05 (Student's t-test)</td>
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</table>

The course and prognosis of occupational asthma after diagnosis has been the subject of several studies. As occupational asthma is defined as reversible airway obstruction due to occupational exposure one could expect that after cessation of the exposure to the particular sensitizing agent the patient should recover. Unfortunately, such a disease course can be observed only in a few cases of occupational asthma. Bronchial hyper-responsiveness and clinical symptoms persist in the majority of patients, although the intensity of the symptoms decreases. The mechanism of the persistence of these changes despite the cessation of occupational exposure is still unknown. The morphological and physiological data concerning this problem are very limited.

In our study a small degree of clinical improvement was noticed that was first apparent due to the fall of daily used beta mimetics and corticosteroids. Also, exercise tolerance seemed to be better in patients re-examined 36 or 48 months after the end of occupational exposure. Questions about the patients' tolerance to physical strain was one of the most important and essential items in the questionnaire. Improvement concerning this parameter could be regarded by the patients themselves as significant but it did not correlate with the results of histamine inhalation test.

The explanation of such a result is not clear-cut. We suppose that certain psycho-sociological aspects could play a significant role here. The first examination had been carried out during diagnosis of the patients, and
therefore in the period when they were receiving financial compensation because of loss of health. Reporting numerous complaints could thus seem reasonable to the subjects. Drug therapy reduction as a health state measure is therefore a more important indicator than the improvement in physical strain tolerance. The authors did not observe significant changes in lung function tests of bakers participating in the study. Some authors suggest that a significant improvement of clinical state and functional tests occurs usually in cases of mild asthma. In our study all subjects were commonly sensitized not only to occupational allergens but also to house dust mite and pollens. Cote et al. in a follow-up study re-examined 48 of 68 workers with red cedar asthma who continued work in the same plant for about 6.5 years after diagnosis. Changes in asthmatic symptoms, treatment requirements, FEV₁ and PD 20 metacholine were assessed. Improvement of clinical status was observed in five of the 48 patients, 25 subjects were stable, 18 deteriorated and none recovered. The results of a follow-up study of 232 subjects with red cedar asthma showed that 81 patients still complained of asthma symptoms 4 years after removal from work. These patients had a longer duration of occupational exposure before the onset of the disease and a longer duration of asthmatic symptoms before diagnosis than the 55 persons who became asymptomatic after the cessation of occupational exposure.

The level of non-specific bronchial hyperreactivity is more strictly correlated with the intensity of airway inflammation and clinical symptoms. In patients with occupational asthma one could expect that the cessation of occupational exposure might influence bronchial hyperreactivity. In our study tolerance to exercise in re-examined patients was a little better, but to our surprise bronchial hyperreactivity to histamine did not significantly change during the study. One could judge however that the slight improvement in clinical state observed in our study would exist with a still-active inflammatory process in bronchial mucosa.

Our data are in contrast to other publications describing the decrease of asthmatic symptoms and NSBH after the cessation of occupational exposure to allergens. On the other hand the persistence of occupational exposure resulted in further deterioration of respiratory function. In 1975 Adams reported that a majority of patients with toluene diisocyanate (TDI)-induced asthma still presented some respiratory symptoms 2-11 years after removal from occupational exposure. Lam et al. observed a significant improvement in NSBH manifested by the increase in the provocative concentration of metacholine needed to cause a 20% fall in FEV₁ (PD20 FEV₁) in patients with occupational asthma several months after cessation of occupational exposure. In 1984 Paggiaro et al. examined 27 workers with TDI-induced asthma. Two years after diagnosis, eight out of 12 subjects who had been completely removed from occupational exposure still complained of dyspnoea. Only in one out of 15 cases in which the exposure to TDI was significantly reduced was a full recovery from asthma attacks observed. Similar results were also reported in other models of occupational asthma, e.g., in asthma due to occupational exposure to red cedar wood or colophony. Chan-Yeung and Desjardins reported the case of four workers employed in a cedar sawmill. Their NSBH had been repeatedly measured within a period of several years before and after they developed occupational asthma. The NSBH was not found before the first symptoms of the disease appeared, but then developed simultaneously with the development of asthma. This indicates that NSBH cannot be regarded as a predisposing risk factor for occupational asthma. No improvement of bronchial hyperactivity indicates that readiness to bronchospasm persists and should also be taken into account in consideration of bronchial disability. Several authors recommend two years after diagnosis as the right moment for the evaluation of the degree of disability in occupational asthma.

The authors did not find a significant difference in the number of positive skin prick tests to flour between the first and second examination after the cessation of occupational exposure. To our surprise previously positive skin tests to occupational allergens were negative in two bakers during the re-examination. The phenomenon of previously positive skin tests becoming negative has been already described by Herxheimer in 1967. One could expect that the persistence of asthma mediated by IgE, even after removal from occupational exposure as in these two bakers could be explained by the persistence of specific serum IgE. This observation is in contrast to a finding by Malo et al. who examined subjects with occupational asthma due to snow crab processing and observed a significant decrease of specific serum IgE several months after cessation of exposure.

Sensitivity to a-amylase was not examined. It seems however that the changes in clinical state and intensity of airway inflammation in re-examined patients could not be due to a-amylase sensitivity, as this allergen is still not a commonly used agent in Polish bakeries.

Smoking has been documented as an important factor influencing clinical status, exercise tolerability and lung function. In our study 15 patients were active smokers at the first examination and eight of them still smoked at re-examination (36-48 months later). The majority of ex-smokers were still passively exposed to tobacco in their homes or other public buildings. Smoking is still a significant problem in Poland. Because of this, a population of Polish bakers may differ from asthmatic bakers from other countries.

**CONCLUSIONS**

The majority of patients with occupational asthma reported subjective improvement in their clinical state 2-3 years after removal from occupational exposure. The intensity of skin prick tests was not significantly reduced in the studied group. Non-specific bronchial hypersensitivity was not significantly reduced in the
majority of subjects with occupational asthma at least 2 years after cessation of occupational exposure.

REFERENCES
