Chapter 10
Occupational Non-immediate Type Allergic Asthma due to Ammonium Persulfate

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Abstract While numerous cases of immediate-type occupational asthma due to persulfates with positive skin prick test reactions to ammonium persulfate are well documented, few non-immediate type reactions have been described in the literature. We report the case of an atopic worker who developed work-related asthmatic symptoms shortly after he began his job in persulfate production. The diagnosis of asthma was corroborated by methacholine testing. The patient showed a positive patch test reaction to ammonium persulfate, while skin prick test was negative. He presented an isolated late symptomatic airway obstruction after a cumulative dose of 0.6 mg ammonium persulfate administered by a dosimeter method. An immunologic mechanism was demonstrated by a significant increase in exhaled nitric oxide and the number of eosinophils in induced sputum. These findings suggest that isolated late bronchial reactions to persulfates are mediated by eosinophilic inflammatory responses.

Keywords Ammonium persulfate • Bronchial challenge • Occupational asthma • Exhaled nitric oxide • Eosinophilic inflammation

10.1 Introduction

An increasing number of published studies over the last decade have associated exposure to persulfates with the development of asthma. Ammonium persulfate (APS) is the predominant substance in this group, and occupational asthma to this low molecular weight substance has been reported among hairdressers as it is widely used in hair bleaches (Pang and Fiume 2001; Moscato et al. 2005). Also, cases among production workers have been described (Munoz et al. 2004).

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The most frequent manifestations are immunologic immediate-type asthmatic reactions and positive skin prick tests (SPT) which have been described repeatedly in the literature. Convincing demonstration of specific IgE antibodies to APS is lacking, although there is a report about an *in vitro* identification of such antibodies (Aalto-Korte and Makinen-Kiljunen 2003). To our knowledge only two case histories of isolated late bronchial reactions to persulfates have been published (Yawalkar et al. 1999; Harth et al. 2006). The underlying mechanism has so far been assumed to be immunologic, but there is still limited information about this.

10.2 Case History

A 32-year old technician in APS production was referred to our institute for an expert medical opinion regarding his respiratory symptoms. The patient complained of asthma attacks, rhinitis, and generalized skin rash starting 2 years before the examination, shortly after his employment in a persulfate production plant, where his tasks involved the bagging of bleaching powders. At the time of diagnosis he had remained away from exposure for 6 months. According to his medical history he had been previously healthy and his symptoms were initially attributed to house dust mite allergy. Although endoscopic ethmoid surgery and hyposensitization against house dust mite was performed, his symptoms did not improve and deterioration of his lung function was described by a pulmonary physician.

While there was no relation of the patient's symptoms with exposure to house dust (mite), the temporal pattern of his symptoms suggested a potential relationship with working tasks involving exposure to APS. Both the respiratory problems and the skin rash occurred more frequently at the workplace and were relieved during weekends and holidays, while they did not change substantially over the different seasons of the year. Initially, the patient was temporarily removed from his workplace because of his symptoms, but the attempt to return to his tasks induced a relapse of the symptoms. The serial peak expiratory flow (PEF) measurements performed by the patient during this trial indicated a significant decrease in PEF parallel to increased symptom scores, during and after working activity, with an increasing difference between morning and evening (post-shift) values (Fig. 10.1).

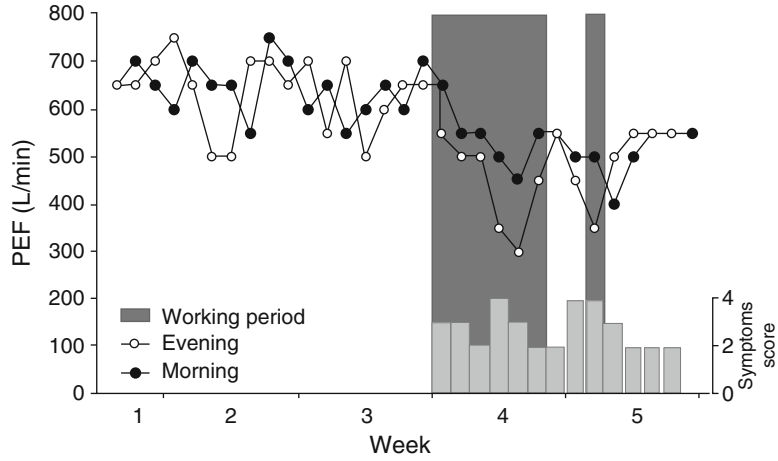

Fig. 10.1 PEF measurements and symptom scores (dyspnea and cough, each graded from 0 (no symptoms) to 4 (strong symptoms) before and during the working period (*shaded areas*). PEF was measured twice daily (morning (*filled dots*) and evening (*open dots*))

10.3 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and was approved by a local Ethics Committee.

The patient underwent a full general medical examination which included basic blood chemistry, blood count, serum protein electrophoresis, semi-quantitative urine examination, total serum IgE, determination of specific IgE antibodies to environmental allergens (ImmunoCAP, Phadia, Freiburg), electrocardiogram and chest X-rays. Body plethysmography, spirometry, diffusion capacity testing, and ergospirometry were performed with equipment from Jäger (Würzburg, Germany). Repeated lung function measurements took place during the first day in order to document a stable respiratory status. Finally, the diagnostic procedure included skin prick testing (SPT) to a battery of environmental allergens (various manufacturers).

APS was bought from Sigma-Aldrich (Deisenhofen, Germany). SPT with APS was performed with a freshly prepared 10% (w/v) solution, and patch testing with an APS preparation from Hermal (Reinbek, Germany). SPT was read at 20 min and the patch test after 24, 48, and 72 h (the patch was removed after 24 h). The inhalation challenge with APS was carried out with the use of a 646-DeVilbiss nebulizer and an APSpro dosimeter (Jäger) with freshly prepared APS in quadrupling doses from 0.4 μg to 0.45 mg (cumulative dose of 0.6 mg; concentrations of 0.01–10 mg/mL). Briefly, each dose was administered in five consecutive slow inspirations from functional residual to near total lung capacity, while the nebulizer was actuated over 0.6 s. Inspiratory airflow was maintained close to 1 L/s by observation of a visual scale. The time interval between consecutive steps was 10 min. The nebulizer was actuated 0.5 s after the start of inspiration to ensure a significant airflow upon nebulization. The response was evaluated by spirometry, body plethysmography (Masterlab, Jäger), exhaled nitric oxide (Lim and Mottram 2008) (eNO; NIOX Flex, Aerocrine, Bad Homburg, Germany), serial methacholine testing, and induced sputum analysis (Quirce et al. 2010).

Methacholine testing was performed with a reservoir method (Baur et al. 1998) (Provotest II; Pari, Starnberg, Germany). The patient was exposed to doubling (cumulative) doses of 31–215 μg methacholine, using a standard solution of 3.3 mg/100 mL. Methacholine testing was done on the day before and 24 h after the specific challenge testing with APS. For each challenge, a provoking dose causing a 20% decline in forced expiratory volume in 1 s ($PD_{20}FEV_1$) was derived by linear interpolation, whereby doses were plotted logarithmically and responses linearly (Crapo et al. 2000). Sputum induction with saline 0.9% and analysis were performed, as described recently (Bacci et al. 1996; Raulf-Heimsoth et al. 2007), immediately before the challenge with APS and about 1 and 24 h afterward. Follow-up measurements of lung function and eNO were carried out after 10 and 30 min, 2 h, hourly from 4 to 6, 24, and 48 h.

10.4 Results

There were no significant abnormal findings in the laboratory values apart from an eosinophilia of 6% in the differential blood count. Total IgE was 702 kU/L. While there were positive SPT reactions to *Dermatophagoides pteronyssinus* and a mixture of grasses (3 mm wheal diameter both), only were specific IgE antibodies to *Dermatophagoides pteronyssinus* and *D. farinae* (CAP-class 2) detected. No significant findings were identified in the patient's resting electrocardiogram and chest X-ray, while ergospirometry revealed no pulmonary limitation. Spirometry showed borderline airway obstruction FEV_1 was 89.4% of predicted and the FEV_1/FVC ratio was 71% with no significant intra-day variability (data not shown).

SPT with APS produced a negative result. In the patch test, after 24 h a slight local erythema was observed which progressed to homogenous erythema and vesicles after 48 h, +++ reaction according to Brasch and Fartasch (2009), and then regressed to a slight erythema at 72 h. While no significant

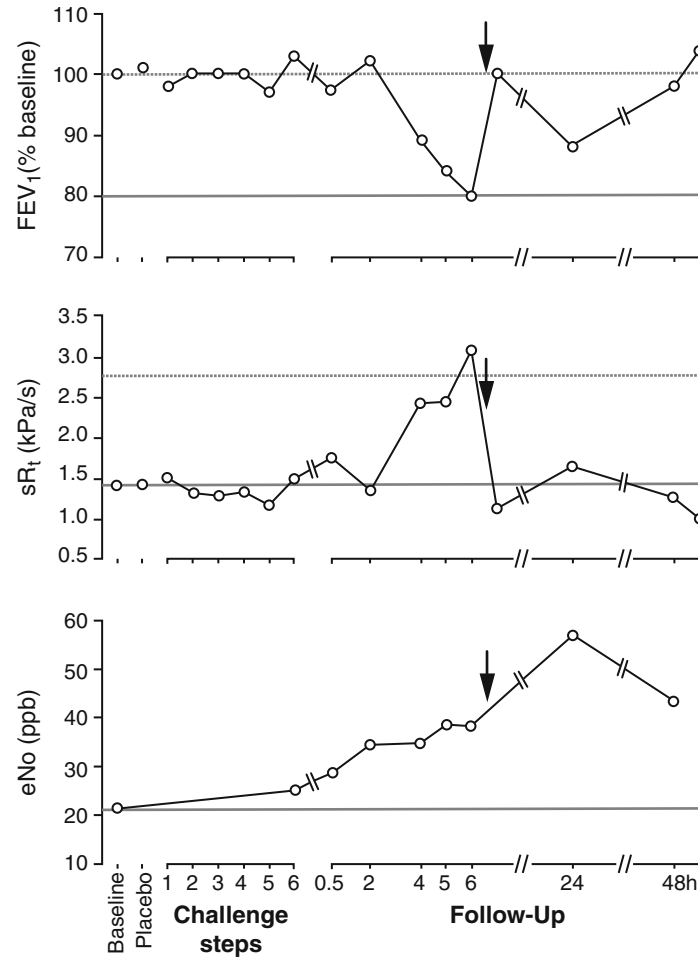

Fig. 10.2 Time-response relationships of FEV_1 (*upper part*), sR_t and eNO (*lower part*) of specific inhalation challenge with ammonium persulfate (APS). Measurements during the challenge represent the values that were obtained 10 min after the application of each APS concentration, for further details see Methods

reaction was observed regarding the patient's lung function parameters during the challenge, 4 h after the test the patient presented symptoms (dizziness and persistent cough), followed by wheezing on auscultation, a 20% fall of FEV_1 from baseline, and an increase of specific airway resistance (sR_t) from 1.43 to 3.08 kPa/s 6 h after the challenge (Fig. 10.2). At that point the patient was administered 300 μg salbutamol to relieve his symptoms and was admitted to the hospital for further monitoring. The respiratory reaction persisted 24 h after the exposure (FEV_1 88% of baseline), while eNO increased from 21 ppb at baseline to 57 ppb (24 h) and 43 ppb (48 h). Baseline $PD_{20}FEV_1$ methacholine (154 μg) was unchanged 24 h after the specific challenge with APS (118 μg).

The total cell numbers in induced sputum were 37×10^5 (baseline), 42×10^5 (30 min), and 50×10^5 (24 h) after the challenge with APS. This corresponded to 5%, 9%, and 12.5% eosinophils, respectively.

10.5 Discussion

Occupational asthma was suspected in this patients based on his work-related symptoms and PEF measurements. The present examination corroborated this diagnosis and identified APS as the causative substance, while house dust mite sensitization was considered of minor importance.

Interestingly, no immediate type reaction could be demonstrated (symptoms, SPT, and inhalation challenge with APS), but a clear isolated late reaction (symptoms, patch test, and inhalation challenge with APS) was observed 4–6 h afterward.

Similar cases of isolated late reactions to APS are extremely rare in the literature. A case of a late asthmatic reaction to APS with a negative SPT has been recently described in a hairdresser by Harth et al. (2006). An immunologic reaction was suggested in that case by positive patch testing and an increase of bronchial hyperresponsiveness after specific inhalation testing with APS. The highest APS concentration in SPT in that study was 1 mg/mL, thus 100-fold lower than in the present study. In the present study, the APS solution was freshly prepared a few minutes before the application to obtain the highest possible sensitivity for the detection of SPT reactions.

Yawalkar et al. (1999) have also reported a case of an isolated late asthmatic reaction which occurred after a nasal challenge with APS. In that case, SPT showed a late reaction 24 h after the application of APS, while the histologic examination demonstrated an infiltration by T lymphocytes at the site of the skin reaction. While a hypothesis of a potential involvement of T lymphocytes has been suggested, a specific methodology to elucidate the immunological background of similar phenomena has not yet been established in the literature. In the present case study, control tests with APS, especially challenge tests, in non-exposed subjects were not performed, because an irritant reaction was not considered likely due to the typical symptoms and the reaction pattern of an isolated late reaction, with an indication of an immunologic mechanism. SPT with the APS solution in ten healthy volunteers were normal (data not shown).

In the present study, the immunologic mechanism was convincingly demonstrated by an increase of eNO and eosinophils in induced sputum after the challenge. Thus, although an isolated late reaction pattern is less common in occupational asthma, an eosinophilic inflammation was shown as the underlying mechanism, as in the case of immediate-type occupational asthma (Sastre et al. 2003). The exact mechanism underlying the simultaneous manifestation of the late respiratory and skin reaction due to APS in our patient is not completely clear. In general, substances that induce contact sensitizations are not considered causative for airways disease. The present, however, demonstrates that this may be not true for persulfates. This is important in clinical practice because patch testing has to be included in the standard diagnostic procedure for patients with suspected occupational asthma due to persulfates and special attention should be paid to the monitoring of bronchial late reactions.

Conflicts of Interest: The authors declare no conflicts of interest in relation to this article.

References

Aalto-Korte, K., & Makinen-Kiljunen, S. (2003). Specific immunoglobulin E in patients with immediate persulfate hypersensitivity. *Contact Dermatitis, 49*(1), 22–25.

Bacci, E., Cianchetti, S., Paggiaro, P. L., Carnevali, S., Bancalari, L., Dente, F. L., Di Franco, A., Giannini, D., Vagaggini, B., & Giuntini, C. (1996). Comparison between hypertonic and isotonic saline-induced sputum in the evaluation of airway inflammation in subjects with moderate asthma. *Clinical and Experimental Allergy, 26*(12), 1395–1400.

Baur, X., Huber, H., Degens, P. O., Allmers, H., & Ammon, J. (1998). Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *American Journal of Industrial Medicine, 33*(2), 114–122.

Brasch, J., & Fartasch, M. (2009). Standardization in Contact Dermatitis – A highly desirable aim. *Contact Dermatitis, 60*(6), 351–352.

Crapo, R. O., Casaburi, R., Coates, A. L., Enright, P. L., Hankinson, J. L., Irvin, C. G., MacIntyre, N. R., McKay, R. T., Wanger, J. S., Anderson, S. D., Cockcroft, D. W., Fish, J. E., & Sterk, P. J. (2000). Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *American Journal of Respiratory and Critical Care Medicine, 161*(1), 309–329.

Harth, V., Raulf-Heimsoth, M., Bruning, T., & Merget, R. (2006). Isolated late asthmatic reaction after exposure to ammonium persulfate in a hairdresser. *Contact Dermatitis, 54*(1), 62–63.

Lim, K. G., & Mottram, C. (2008). The use of fraction of exhaled nitric oxide in pulmonary practice. *Chest, 133*(5), 1232–1242.

Moscato, G., Pignatti, P., Yacoub, M. R., Romano, C., Spezia, S., & Perfetti, L. (2005). Occupational asthma and occupational rhinitis in hairdressers. *Chest, 128*(5), 3590–3598.

Munoz, X., Cruz, M. J., Orriols, R., Torres, F., Espuga, M., & Morell, F. (2004). Validation of specific inhalation challenge for the diagnosis of occupational asthma due to persulphate salts. *Occupational and Environmental Medicine, 61*(10), 861–866.

Pang, S., & Fiume, M. Z. (2001). Final report on the safety assessment of ammonium, potassium, and sodium persulfate. *International Journal of Toxicology, 20*(Suppl 3), 7–21.

Quirce, S., Lemiere, C., de Blay, F., del Pozo, V., Gerth Van Wijk, R., Maestrelli, P., Pauli, G., Pignatti, P., Raulf-Heimsoth, M., Sastre, J., Storaas, T., & Moscato, G. (2010). Noninvasive methods for assessment of airway inflammation in occupational settings. *Allergy, 65*(4), 445–458.

Raulf-Heimsoth, M., Pesch, B., Schott, K., Kappler, M., Preuss, R., Marczynski, B., Angerer, J., Rihs, H. P., Hahn, J. U., Merget, R., & Bruning, T. (2007). Irritative effects of fumes and aerosols of bitumen on the airways: Results of a cross-shift study. *Archives of Toxicology, 81*(1), 35–44.

Sastre, J., Vandenplas, O., & Park, H. S. (2003). Pathogenesis of occupational asthma. *European Respiratory Journal, 22*(2), 364–373.

Yawalkar, N., Helbling, A., Pichler, C. E., Zala, L., & Pichler, W. J. (1999). T cell involvement in persulfate triggered occupational contact dermatitis and asthma. *Annals of Allergy, Asthma & Immunology, 82*(4), 401–404.