

CASE REPORT

Occupational asthma and rhinitis caused by 1,2-benzisothiazolin-3-one in a chemical worker

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We report a case of occupational asthma and rhinitis caused by inhalation of 1,2-benzisothiazolin-3-one, an additive used as a microbicide in detergent production, in a 26-year-old man employed in a chemical factory producing detergents. The subject's task consisted of pouring raw materials into the recipient of a machine which mixed the substances. Two months after the beginning of this job the patient complained of rhinitis and asthma at the workplace. The specific challenge test with 1,2-benzisothiazolin-3-one, one of the raw materials to which the subject was exposed, provoked an immediate prolonged asthmatic response and nasal symptoms, whereas exposure to other agents (e.g., α -amylase, alcalase or bezalkonium chloride) to which the patient was also exposed at work did not. To our knowledge this is the first case of occupational asthma and rhinitis caused by this compound.

Key words: Bronchial challenge; detergent industry; low molecular weight compounds; occupational asthma.

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INTRODUCTION

In the detergent industry several cases of occupational asthma to high molecular weight compounds, and to a lesser extent low molecular weight compounds, have been described.¹

In this paper we report a case of occupational asthma and rhinitis caused by the inhalation of 1,2-benzisothiazolin-3-one, a low molecular weight aromatic ketone which is used as a microbicide in the production of detergents. This compound is known to be an eye and skin irritant and has been reported to cause skin sensitization.²⁻³ To our knowledge this is the first report of occupational asthma and rhinitis caused by inhalation of this substance.

SUBJECT

A 26-year-old man was referred to our department because of suspected occupational asthma and rhinitis. He had worked as a messenger in a bank from the age of 16–20 years and in a plant that worked metal from 20–23 years of age. At age 23 he began working in a chemical factory that produced detergents. He was first assigned to the packaging department for one year, then the job of plant controller. One of his duties was to pour loads of liquid raw materials (about eleven kilograms each load) into the feed chute of a machine which later mixed the substances. The machine was equipped with a local exhaust fan on the feed chute. The procedure was repeated three times during each work shift for two weeks every month. During the job the patient wore protective gloves and goggles. The raw materials included several components used in the production of detergents, i.e., enzymes (alcalase, α -amylase), tensio-actives polyacrylic acid, disinfectants (benzalkonium chloride)

and 1,2-benzisothiazolin-3-one (an additive used as a microbicial in detergent production).

Two months after beginning the new job the patient started experiencing nasal itching and stuffiness, tearing, ocular burning and dry cough at the workplace. Three months later sputum, dyspnoea and chest tightness appeared. Symptoms presented when the patient poured the raw materials into the machine; the symptoms spontaneously disappeared within 15–30 min. If the subject proceeded with the task then the symptoms persisted throughout the day, and sometimes appeared in the evening when away from work. Symptoms resolved promptly after treatment with inhaled salbutamol. The patient had never complained of the above symptoms before being employed at this job.

The patient came to our observation one year after having been assigned the job of plant controller. He had worked under usual work conditions until two days before his admission to the hospital. At the time of admission he did not complain of respiratory symptoms and was not receiving treatment. He was an ex-smoker and had no previous personal or family history of allergic disease. Physical examination, chest radiograph and ECG were normal. Laboratory tests revealed mild blood eosinophilia (7%). The paranasal sinus radiograph showed bilateral mucoperiosteal thickening and deviation of the nasal septum. Basal lung function tests showed forced expiratory volume (FEV-1) of 107% predicted and vital capacity (VC) of 108% predicted. Both skin tests and the serum specific IgE levels for the more common pneumoallergens were negative. Total IgE were in the normal range. PD20 FEV-1 of methacholine was greater than 3400 mcg, indicating normal bronchial responsiveness, and ultrasonically nebulized distilled water challenge⁴ was negative.

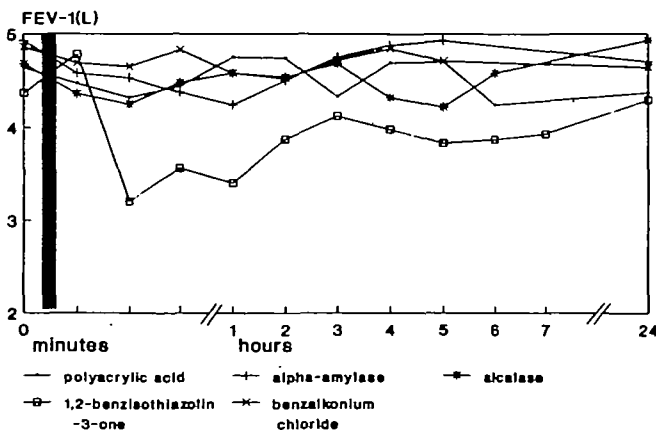
Specific challenges were carried out with different substances to which the patient was exposed at work (one challenge/day with a two day interval between each test). Each challenge was carried out in a static 7.2 cubic metre exposure chamber equipped for rapid air exchange.⁴ A fan in the chamber ensured adequate

mixing and circulation. Spirometry was performed before and at 5, 15, 30 and 60 min and hourly for 7 h after exposure. At the same time-points, peak expiratory flow (PEF) was registered.⁵ After 7 h, PEF registration was continued by the patient throughout the evening (every hour) with the recommendation to measure PEF at any time symptoms occurred. A challenge was considered positive when a decrease in FEV-1 of 15% or greater, or a decrease in PEF values of at least 60–70 L/sec or greater from baseline was observed.⁵ On days 1, 2, 3 and 4 the patient was challenged in the inhalation chamber with alcalase (exposure for 20 min to an atmosphere containing 6×10^{-5} mg/m³), α -amylase (exposure for 20 min to a nebulized 0.1% aqueous solution), benzalkonium chloride (by pouring a 10% aqueous solution from one beaker to another for 30 min), and polyacrylic acid (exposure for 20 min to a nebulized 0.2% aqueous solution) respectively. No significant variation in pulmonary function was observed on any of the challenge days.

On day 5 the patient was exposed to a nebulized 0.04% aqueous solution of 1,2-benzisothiazolin-3-one at room temperature for 20 min. The challenge provoked an immediate prolonged asthmatic response with a maximum 26% FEV-1 fall at 15 min; nasal symptoms referred by the patient at the workplace were also reproduced. FEV-1 spontaneously returned to baseline values 2 h after the exposure. No late response was observed in the laboratory up to 7 h later nor during the night (Figure 1). To exclude an irritant effect of the concentration of 1,2-benzisothiazolin-3-one used during the challenge, two hyperresponsive subjects with normal lung function tests and no previous exposure to this compound were challenged. The first subject was a 25-year-old nonatopic man with occupational asthma due to phtalic anhydride, diagnosed by specific bronchial challenge. FEV-1 was 98% and VC 104% of predicted and PD20 FEV-1 to methacholine was 63 mcg. The second subject was a 33-year-old woman with allergic rhinitis and mild asthma due to mites. FEV1 was 101% and VC 103% of predicted, PD20 FEV1 to methacoline was 340 mcg. The former did not receive therapy, the latter was treated with nedocromil sodium 8 mg/day and salbutamol as needed. The therapy was interrupted 48 h prior to the challenge with 1,2-benzisothiazolin-3-one. No bronchospastic response was obtained. Since 1,2-benzisothiazolin-one is known to release formaldehyde when heated (L. Bernstein, personal communication, AAI International Conference, New York, USA, 23 February–1 March 1995), one week later the patient was submitted to specific challenge with formaldehyde,⁶ and venous blood was drawn for the assessment of specific IgE to formaldehyde in the serum. No response to the challenge was obtained and the assessment of specific IgE was negative as well.

Occupational asthma and rhinitis caused by 1,2-benzisothiazolin-3-one were diagnosed, and the patient was discharged with the recommendation to avoid

Figure 1. Time course of the specific bronchial challenges with the substances used at work in the subject studied.



further exposure to 1,2-benzisothiazolin-3-one.

Approximately one month after the diagnosis the patient was removed from exposure and relocated in the same factory. He was assigned the position of warehouse keeper. At 1- and 3-month follow-up visits, pulmonary function and bronchial responsiveness to methacholine were substantially unchanged. The patient continued to experience nasal and bronchial symptoms when he passed in the vicinity of the machine in which the raw materials containing 1,2-benzisothiazolin-3-one were poured.

DISCUSSION

The patient history and the respiratory response to specific challenge with 1,2-benzisothiazolin-3-one fulfilled the criteria for the diagnosis of occupational asthma and rhinitis due to this substance.⁷

The molecule 1,2-benzisothiazolin-3-one is a low molecular weight aromatic ketone containing a benzene group, a ketone group and an alkyl group, and it is used as an additive in the production of detergents. This compound is known to be an eye and skin irritant and is harmful if swallowed; it is also known to cause cutaneous sensitization²⁻³ but to our knowledge there has been no previous report of occupational asthma or rhinitis due to this compound.¹

The patient in the case described had a history suggestive of occupational asthma with a latency period, as defined by Bernstein *et al.*:⁸ the patient had never complained of asthma symptoms before starting the job of plant controller in the chemical factory and the symptoms appeared after six months at the new job. As reported in several cases of occupational asthma,⁷ bronchial responsiveness to methacholine and ultrasonic 'fog' was negative at the time of diagnosis. The challenge with 1,2-benzisothiazolin-3-one reproduced the nasal and bronchial symptoms experienced by the patient at the workplace. Symptoms appeared immediately after exposure and resolved about 1 h after terminating exposure. Pulmonary function spontaneously returned to baseline 2 h after the end of exposure. No late response was observed during the specific challenge. Unfortunately, no data were available regarding exposure levels at the workplace. Since exposure to 1,2-benzisothiazolin-3-one has no recommended threshold limit values, we challenged two hyper-responsive subjects with no previous history of occupational exposure to this compound so as to exclude possible irritating effects to the compound. Having obtained no nasal or bronchial response, we concluded that a non-specific response to this compound would be very unlikely. The absence of a response to other compounds to which the patient was

exposed at the workplace, indirectly provides strong support for the specificity of the response to 1,2-benzisothiazolin-3-one, inasmuch as alkalase and α -amylase, which are well known respiratory sensitizers, failed to produce a response upon challenge.⁷

The mechanism underlying the respiratory response has not been elucidated. The specific challenge with formaldehyde, a substance known to be released when 1,2-benzisothiazolin-3-one is heated (L. Bernstein, personal communication, AAAI International Conference, New York, USA, February 23–March 1, 1995), was negative. The detection of specific IgE against formaldehyde in the serum was negative as well. The clinical features, the presence of a latency period between the beginning of occupational exposure and onset of symptoms,⁸ the symptom time-course at the workplace and the simultaneous presence of bronchial and nasal response to the specific bronchial challenge suggest an immunologic mechanism. Unfortunately, at present there is no specific test that can demonstrate the pathophysiologic mechanism involved in occupational asthma due to low molecular weight compounds.

In conclusion, we have described a case of occupational asthma and rhinitis due to 1,2-benzisothiazolin-3-one. This compound should be listed as one of the low molecular weight agents that cause occupational asthma.

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