Case Report

Occupational asthma due to piperazine citrate

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Summary. *Background:* Piperazine is a secondary heterocyclic amine that may give rise to occupational asthma of uncertain mechanism.
Methods: We report on a 42-year-old woman, a process operator in a chemical factory, who developed work-related symptoms of rhinitis and asthma upon exposure to piperazine citrate. She remained symptom free during holidays and days off work.
Results: Skin prick test with piperazine citrate was positive. Specific inhalation challenge with piperazine citrate at a concentration of 5 mg/m^3 for 30 minutes elicited an isolated late asthmatic response. Airway hyperresponsiveness to methacholine significantly increased 3 hours after the piperazine challenge, preceding the late asthmatic response.
Conclusion: This patient had developed occupational asthma caused by piperazine, as confirmed by the specific inhalation challenge test, possibly due to an immunological mechanism.

Key words: Occupational asthma, piperazine, amines, specific inhalation challenge.

Resumen. La piperazina es una amina heterocíclica secundaria que puede producir asma profesional de mecanismo desconocido.
Métodos: Se estudió el caso de una mujer de 42 años de edad, empleada como operadora de proceso en una fábrica química, que desarrolló síntomas de rinitis y asma relacionados con la actividad laboral tras la exposición a citrato de piperazina. Durante las vacaciones y los días libres no experimentó síntomas.
Resultados: El prick test con citrato de piperazina obtuvo un resultado positivo. La prueba de provocación por inhalación específica con citrato de piperazina a una concentración de 5 mg/m^3 durante 30 minutos puso de manifiesto una respuesta asmática tardía aislada. La hiperreactividad bronquial a la metacolina aumentó de forma significativa al cabo de 3 horas tras la prueba de provocación con piperazina, que precedió a la respuesta asmática tardía.
Conclusión: Esta paciente desarrolló asma profesional causada por la piperazina, tal como confirmó la prueba de provocación por inhalación específica, posiblemente debido a un mecanismo inmunológico.

Palabras clave: asma profesional, piperazina, aminas, provocación por inhalación específica.

Case report

We report on a 42-year-old woman, a non-smoker, who had worked as a process operator in a chemical factory since 1973. At work, she handled, weighed and packed several chemical products and drugs in batches. In 1995 she developed work-related symptoms of cough, chest tightness, shortness of breath and wheezing as well as nasal stuffiness, watery nose, and nasal and ocular itching. Her symptoms were mild and intermittent until October 1998, when she suffered from persistent asthma despite the fact that she wore a respirator at work. Asthma symptoms occurred mostly in the evening or at night, several hours after her work shift. She noticed that these episodes developed after handling piperazine citrate. She was symptom free during holidays and days off work.

Methods and results

Blood differential cell count and chest and paranasal sinus x-rays showed no abnormalities. Spirometry revealed a FVC of 4.07 L (132% predicted), FEV_1 of 3.38 L (129% predicted), and FEV_1/FVC of 83%. Total serum IgE was 10 kU/L. Skin prick tests with a battery of common aeroallergens (*Cupressus arizonica*, *Lolium*

perenne, Platanus acerifolia, Olea europaea, Salsola kali, Plantago lanceolata, and *Artemisia vulgaris* pollen, *Dermatophagoides pteronyssinus* and *D. farinae*, cockroaches, cat and dog dander, *Alternaria alternata*, *Aspergillus fumigatus* and natural rubber latex) from ALK-Abelló (Madrid, Spain) were all negative. Skin prick test with piperazine citrate (10 mg/ml) elicited a positive reaction (5 mm wheal) in the patient, whereas it was negative in 5 control subjects. Methacholine inhalation test demonstrated airway hyperresponsiveness (PC_{20} 1 mg/ml).

A controlled specific inhalation challenge (SIC) test was carried out in a closed-circuit system for exposure to particles as previously reported [1]. The aerosol was inhaled by the patient at tidal volume. During aerosolization, powder concentration was measured in real time. As a control bronchial challenge the patient was exposed to lactose powder (10 mg/m^3 for 15 minutes). The following day increasing concentrations of piperazine citrate powder were given by inhalation. The dose was increased at intervals of 10 minutes and FEV_1 and FVC were measured at 5 and 10 minutes after inhalation of each concentration. The inhalation challenge test was discontinued when there was a fall in FEV_1 of 20% or greater from baseline value, or when the highest concentration had been given. After exposure to a concentration of 5 mg/m^3 for 30 minutes, she developed rhinitis symptoms and an isolated late asthmatic reaction was observed (Figure 1). A methacholine challenge test performed 3 hours after SIC showed a significant increase in airway hyperresponsiveness (PC_{20} 0.13 mg/ml).

Discussion

It is known that exposure to the heterocyclic amine piperazine may induce occupational asthma [2-4]. The presence of IgE antibodies against a conjugate between human serum albumin and piperazine has been previously demonstrated in some patients with piperazine-induced asthma [5,6]. Pepys et al. [2] described isolated late asthmatic reactions after SIC with piperazine in two subjects. Late asthmatic responses induced by high and low molecular weight agents are associated with an increase in airway hyperresponsiveness to pharmacological agents (methacholine, histamine) that occurs 6-8 hours after exposure and return to baseline level within a period of 24 hours to 4 weeks [7]. Nevertheless, this increase in airway hyperresponsiveness may precede the late asthmatic response [8,9], as we observed in our patient 3 hours after SIC to piperazine. This finding suggests that airway changes that underlie the late asthmatic reaction may occur before this response becomes clinically apparent.

This patient developed an isolated late asthmatic response (although an incipient early asthmatic reaction was also noted) after SIC to piperazine, despite the fact that she had a positive skin prick test to piperazine. This intriguing fact, however, has also been observed with other low and high molecular weight agents that act through an IgE-dependent mechanism [7].

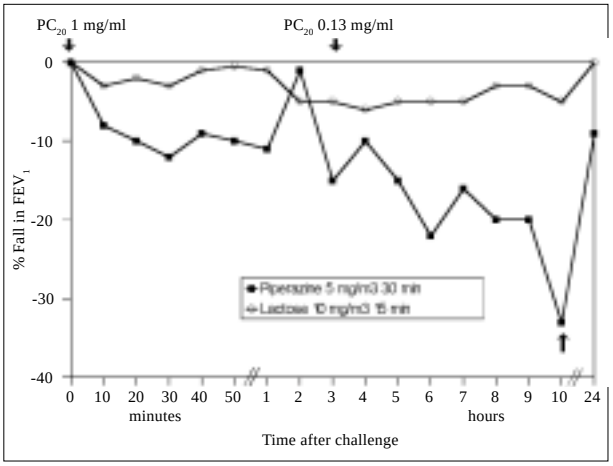

Figure 1. Specific inhalation challenge to piperazine in a closed-circuit system for exposure to particles. Increased airway hyperresponsiveness to methacholine was observed 3 hours after the piperazine challenge, preceding the isolate late asthmatic response.

References

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