
Case report

Occupational asthma related to aescin inhalation

Xavier Muñoz, PhD*†; Mario Culebras, MD†; Maria-Jesus Cruz, PhD†; and Ferran Morell, PhD†

Background: More than 400 agents are recognized as causes of occupational asthma, a work-related disease that can be induced by an immunologic or a nonimmunologic mechanism.

Objective: To describe a 57-year-old man employed in the pharmaceutical industry who developed bronchial asthma while working with products such as *Plantago ovata* and aescin, an active ingredient with anti-inflammatory and venotonic properties.

Methods: Various tests were performed, including radiography, total serum IgE titer measurements, skin tests against common pneumoallergens and *Plantago* species, pulmonary function studies, a methacholine test, and specific inhalation challenge with *P ovata* and aescin.

Results: The results of these tests, including specific inhalation challenge, confirmed the diagnosis of occupational asthma due to aescin exposure, whereas the results of specific challenge with *P ovata*, a known cause of occupational asthma, were negative.

Conclusions: Aescin may represent a new causative agent of occupational asthma in personnel working in the pharmaceutical industry. The mechanism by which aescin can produce asthma is unknown, but analysis of the characteristics of our patient suggests a non-IgE immunologic mechanism, although an irritative mechanism secondary to long-term low-level exposure to aescin, a possible irritant, cannot be ruled out.

Ann Allergy Asthma Immunol. 2006;96:494–496.

INTRODUCTION

Occupational asthma (OA) is a work-related disease that is more frequent in developed countries.¹ More than 400 agents are recognized causes of this condition,² which can be induced by an immunologic or a nonimmunologic mechanism. Immunologic OA is characterized by a period of latency before the onset of symptoms and can be mediated by IgE antibody–dependent or non–IgE-dependent mechanisms, some of which are still uncertain.³ Nonimmunologic asthma has classically been associated with reactive airway dysfunction syndrome, which is produced when a person is acutely exposed to high doses of an irritant agent.⁴ It has recently been suggested that long-term low-level exposure to irritants for days, weeks, or even years^{5–7} can also be a cause of asthma. Some researchers^{6,7} have suggested the terms *not-so-sudden irritant-induced asthma* and *low-dose reactive airway dysfunction syndrome* to name this entity.

Exposure to various pharmacologic agents in the work environment has been implicated in the development of OA in pharmaceutical industry workers.⁸ In the present study, we describe a patient with bronchial asthma caused by exposure to aescin, an active ingredient with anti-inflammatory and venotonic properties used in the manufacture of drugs to treat varicose veins, hemorrhoids, and postoperative edema.⁹ Some cases of contact dermatitis have been described after topical

application of this active ingredient¹⁰; however, there are no references to date, to our knowledge, of respiratory symptoms in workers exposed to this substance. Aescin is a mixture of more than 30 different saponins and is the active ingredient in *Aesculus hippocastanum* (horse chestnut), a tree found all over the world. The seeds of this tree contain up to 60% of this substance.⁹ Some studies^{11,12} have shown that specific saponins can mitigate allergic effects, but there is also a reported case of asthma induced by saponins derived from *Quillaja saponaria*, a tree whose inner bark is used to extract saponins for the production of detergents.¹³ Herein we describe the first case of OA secondary to environmental exposure to aescin in a pharmaceutical industry worker and discuss the possible pathogenic mechanisms implicated in the origin of this case.

CLINICAL CASE

The patient, a 57-year-old man, was an ex-smoker for 5 years with a former cigarette habit of 20 pack-years and no other toxic habits or known medical allergies. His clinical history included dyslipidemia, hypothyroidism, and ulcerative colitis. He had been working for 30 years in the pharmaceutical industry in contact with aescin and, for the previous 5 years, *Plantago ovata*. The patient's task at the workplace consisted of weighing the various products used in the manufacture of medicinal drugs and placing them in different receptacles. This task was performed in room air without the use of respiratory protection measures, which means that the patient might have been exposed to daily inhalation of low doses of these agents. The patient referred to symptoms of dry cough, dyspnea, sibilant wheezing, oppressive chest discomfort, and

* Departamento de Biología Celular, Fisiología e Inmunología, Facultad de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain.

† Servicio de Neumología, Hospital Vall d'Hebron, Barcelona, Spain.

Received for publication May 31, 2005.

Accepted for publication in revised form July 17, 2005.

rhinitis occurring during the past 10 years, which had become aggravated in recent years coinciding with exposure to *P ovata*. He had gone to the emergency department on 15 occasions for acute episodes of bronchospasm, and he required 2 hospitalizations. The symptoms were clearly related to the work environment because they improved during the weekend and vacation periods and while on sick leave from work.

The chest radiograph showed only slight degenerative changes in the dorsal column. Blood test results were normal, with total serum IgE titers less than 10 kU/L and negative results for *Plantago* species. Results of skin tests against common pneumoallergens and *Plantago* species were negative, and results of pulmonary function studies were normal, with a forced vital capacity (FVC) of 4.82 L (101%), a forced expiratory volume in 1 second (FEV₁) of 3.78 L (106%), an FEV₁/FVC ratio of 78%, and a negative bronchodilation test result. The methacholine test result was positive, with a provocation concentration that caused a decrease in FEV₁ of 20% (PC₂₀) of 1 mg/mL. Maximum flow recording performed by the patient while at work showed variability higher than 20% and improvement during periods of sick leave from the workplace. Visual interpretation of the recording was consistent with a diagnosis of OA. On the basis of suspected OA, the patient underwent specific inhalation challenge (SIC) according to the method proposed by Pepys and Hutchcroft¹⁴ after giving written informed consent for the test.

Briefly, on the first day, 10 g of *P ovata* was mixed with 150 g of lactose and was tipped from one tray into another 30 cm away from the patient's face for 15 minutes in a challenge booth with independent air extraction. The test result was negative, and PC₂₀ measurement after exposure showed no changes with respect to the baseline value. On the second

day, the patient was exposed to 5 g of aescin mixed with 150 g of lactose in the same manner for 5 minutes. The test result was positive, with the patient showing a 30% decline in FEV₁ 45 minutes after exposure and symptoms of bronchospasm that required the administration of bronchodilators (Fig 1). No changes in FEV₁ were observed in response to a control challenge of lactose powder alone conducted on a separate day.

The diagnosis of OA due to aescin was established, and the patient was advised to avoid the causal agent. Since this measure was taken, the patient has remained asymptomatic and has not required emergency department visits or hospitalization. Results of a follow-up pulmonary function study at 6 months were normal, and the methacholine test showed improvement of bronchial hyperresponse, with a PC₂₀ of 6 mg/mL.

DISCUSSION

Psyllium, a product derived from the seed and hull of *P ovata*, is a potent occupational allergen that affects pharmaceutical industry workers and health care professionals.^{15–17} The frequency of sensitization in pharmaceutical workers exposed to this agent has been estimated to be 32%,¹⁷ although the prevalence of OA in this population is close to 4%.^{16–18} Because the patient in the present study had been exposed to this substance and did not mention any other substance known to produce OA, *P ovata* was first suspected as the causal agent of his asthma. Nevertheless, the results of immunologic tests, specific IgE measurements, skin tests, and SIC ruled out this possibility. Furthermore, although the patient's symptoms were exacerbated after initiating contact with *P ovata*, he had first experienced the symptoms long before.

The patient was also exposed to aescin. Although no cases of asthma caused by exposure to this substance have been described in the literature, one report¹³ of a patient with respiratory symptoms due to *Q saponaria* exposure led us to consider that aescin, a mixture of several saponins, might be causing the symptoms in our patient. This possibility was confirmed by positive SIC results and by resolution of the symptoms and decreased sensitivity documented by the methacholine test (increased PC₂₀) after discontinuing exposure to this agent at the workplace.

The onset of symptoms occurred 20 years after initiating exposure, and the symptoms became aggravated in the 2 years before consulting. This period of latency leads us to consider an immunologic mechanism in this case of OA. Furthermore, the presence of low levels of total IgE and the type of response observed in the SIC (an early and sustained reaction), could support a non-IgE-dependent immunologic mechanism. Nevertheless, the fact that the patient weighed the products without the use of respiratory protection measures indicates that he might have been exposed to daily inhalation of low doses of these agents. Hence, we cannot rule out the possibility that this OA was induced by exposure to low doses of an irritating agent. Aescin, as a saponin and

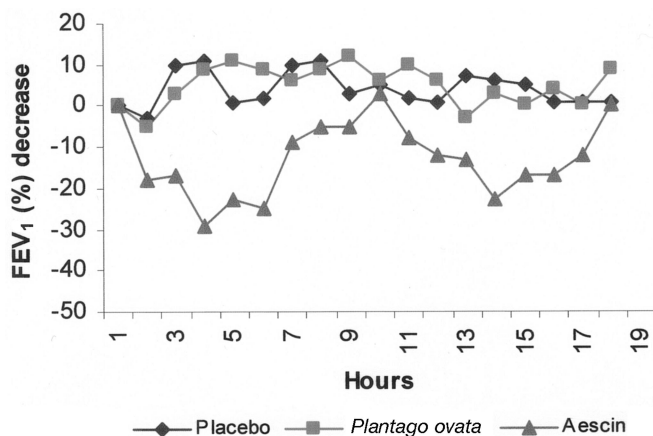


Figure 1. Results of specific inhalation challenge with *Plantago ovata* (10 g per 150 g of lactose), aescin (3 g per 150 g of lactose), and placebo (150 g of lactose). No significant changes in forced expiratory volume in 1 second (FEV₁) were observed when the patient was exposed to *P ovata*. An asthmatic reaction with a significant decline in FEV₁ was noted 45 minutes after the patient was exposed to aescin.

surfactant agent, can act as an irritant in the same manner as has been described for other surfactant agents in the detergent industry.^{19,20} Furthermore, the type of reaction observed in the SIC did not differ from that seen in some cases of OA due to isocyanates, in which an irritative mechanism could also be present when the threshold limit value is exceeded.²¹ Not-so-sudden irritant-induced asthma is still a poorly defined entity characterized by a period of latency that can vary from days to years,⁵⁻⁷ as occurred in our patient, and it can be difficult to differentiate from non-IgE-mediated immunologic OA. The mechanisms by which it is produced are largely unknown, but a localized airway inflammatory response is likely to be involved. It has been hypothesized that irritant-induced epithelial damage is followed by direct activation of nonadrenergic, noncholinergic pathways via axon reflexes and the onset of neurogenic inflammation. Nonspecific macrophage activation and mast cell degranulation may also occur.²²

In conclusion, aescin may represent a new occupational agent in personnel working in the pharmaceutical industry. The mechanism by which aescin can produce asthma is unknown, but analysis of the characteristics of our patient suggests a non-IgE immunologic mechanism, although an irritative mechanism secondary to long-term low-level exposure to aescin, a possible irritant, cannot be ruled out. It is important to be aware of these infrequent entities because the most suitable treatment may be avoidance of the causal agent. This was true in our patient, in whom symptoms disappeared and the grade of bronchial hyperresponse decreased after discontinuation of aescin exposure.

REFERENCES

- Meredith S, Nordman H. Occupational asthma: measures of frequency from four countries. *Thorax*. 1996;51:435-440.
- AsmaPro database: clinique des maladies respiratoires. Available at: <http://www.asmanet.com>. Accessed October 5, 2005.
- Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med*. 1995;333:107-112.
- Alberts WM, do Pico GA. Reactive airways dysfunction syndrome. *Chest*. 1996;109:1618-1626.
- Bherer L, Cushman R, Courteau JP, et al. Survey of construction workers repeatedly exposed to chlorine over a 3 to 6 month period in a pulpmill, II: follow-up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended. *Occup Environ Med*. 1994;51:225-228.
- Brooks SM, Hammad Y, Richards I, Giovenco-Barbas J, Jenkins K. The spectrum of irritant-induced asthma: sudden and not-so-sudden and the role of allergy. *Chest*. 1998;113:42-49.
- Kipen HM, Blume R, Hutt D. Asthma experience in an occupational and environmental medicine clinic: low-dose reactive airways dysfunction syndrome. *J Occup Med*. 1994;36:1133-1137.
- Malo JL, Bernstein IL. Other chemical substances causing occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein D, eds. *Asthma in the Work Place*. 2nd ed. New York, NY: Marcel Dekker Inc; 1999:523-541.
- Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. *Pharmacol Res*. 2001;44:183-193.
- Escribano MM, Muñoz-Bellido FJ, Velásquez E, et al. Contact urticaria due to aescin [case report]. *Contact Dermatitis*. 1997;37:233.
- Akagi M, Fukuishi N, Kan T, Sagesaka YM, Akagi R. Anti-allergic affect of tea-leaf saponin (TLS) from tea leaves (*Camellia sinensis* var. *sinensis*). *Biol Pharm Bull*. 1997;20:565-567.
- Park KH, Park J, Koh D, Lim Y. Effect of saikosaponin-A, a triterpenoid glycoside, isolated from *Bupleurum falcatum* on experimental allergic asthma. *Phytother Res*. 2002;16:359-363.
- Raghuprasad PK, Brooks SM, Litwin A, Edwards JJ, Bernstein IL, Gallagher J. Quillaja bark (soapbark)-induced asthma. *J Allergy Clin Immunol*. 1980;65:285-287.
- Pepys J, Hutchcroft BJ. Bronchial provocation test in aetiology diagnosis and analysis of asthma. *Am Rev Respir Dis*. 1975;112:829-859.
- Vaswani SK, Hamilton RG, Valentine MD, Adkinson NF. Psyllium laxative-induced anaphylaxis, asthma and rhinitis. *Allergy*. 1996;51:266-268.
- Malo JL, Cartier A, L'Archeveque J, et al. Prevalence of occupational asthma and immunologic sensitization to psyllium among health personnel in chronic care hospitals. *Am Rev Respir Dis*. 1990;142:1359-1366.
- Brady JD, Malo JL, Seguin P, Gezzho H. Occupational asthma and IgE sensitization in a pharmaceutical company processing psyllium. *Am Rev Respir Dis*. 1987;135:1033-1038.
- Mark GB, Salome CM, Woolcock AJ. Asthma and allergy associated with occupational exposure to *ispaghula* and senna products in a pharmaceutical work force. *Am Rev Respir Dis*. 1991;144:1065-1069.
- Brant A, Hole A, Cannon J, et al. Occupational asthma caused by cellulase and lipase in the detergent industry. *Occup Environ Med*. 2004;61:793-795.
- Sarlo K. Control of occupational asthma and allergy in the detergent industry. *Ann Allergy Asthma Immunol*. 2003;90(suppl 2):32-34.
- Tarlo SM, Liss GM. Diisocyanate-induced asthma: diagnosis, prognosis, and effects of medical surveillance measures. *Appl Occup Environ Hyg*. 2002;17:902-908.
- Gautrin D, Bernstein IL, Brooks S. Reactive airways dysfunction syndrome, or irritant-induced asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, et al, eds. *Asthma in the Work Place*. 2nd ed. New York, NY: Marcel Dekker; 1999:565-593.

Requests for reprints should be addressed to:

Xavier Muñoz, PhD
Servicio de Neumología
Hospital General Vall d'Hebron
Passeig Vall d'Hebron
119
08035 Barcelona, Spain
E-mail: xmunoz@vhebron.net