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Case report

Occupational asthma and anaphylaxis due to seeds of *Plantago ovata*

Background: The seeds of *Plantago ovata* (*Psyllium*, *Ispaghula*) used in the preparation of bulk laxatives, are well known causes of occupational asthma and anaphylaxis. We report the immunological study of a worker from the pharmaceutical industry who developed occupational asthma in relation to exposure to *Plantago ovata* seeds and an anaphylactic reaction following their ingestion. **Case report:** A 31-year-old man presented with rhinitis and wheezing in association with his work and exposure to seeds of *Plantago ovata*. The patient also suffered from an episode of bronchoconstriction, abdominal pain, facial angioedema, and generalized urticaria following ingestion of the laxative. **Results:** Cutaneous tests against different environmental respiratory allergens (home dust mites, cat and dog epithelium mites) were positive as well as skin tests with *Plantago ovata* extract. Specific IgE (EIA and CAP system) against *Plantago ovata* was positive and SDS-PAGE immunoblotting (Western blot) showed IgE bands of 78, 59, 34, 25, and 17,6 kDa, respectively. Basal rhinomanometry and a specific nasal challenge test against *Plantago ovata* were positive. **Conclusions:** Sensitization to *Plantago ovata* is relatively common among workers exposed by inhalation (health care and pharmaceutical industry personnel). Sensitized individuals have an important risk for severe anaphylactic reactions after ingestion of this substance.

Key words: Occupational asthma. Anaphylaxis. *Plantago ovata*.

Asma ocupacional y anafilaxia por semillas de *Plantago ovata*

Fundamento: Las semillas de *Plantago ovata* (*Psyllium*, *Ispaghula*), utilizadas en la preparación de laxantes de volumen, son conocidas como causantes de asma ocupacional y anafilaxia. Se presenta el estudio inmunológico de un trabajador de una industria farmacéutica que desarrolló asma ocupacional en relación con la exposición a semillas de *Plantago ovata* y una reacción anafiláctica posterior a su ingesta. **Observación clínica:** Varón de 31 años de edad que consultó por presentar rinitis asociada a sibilantes, en relación con la jornada laboral y la exposición a semillas de *Plantago ovata*. También refirió un episodio de broncospasmo, dolor abdominal, angioedema facial y urticaria generalizada posterior a la ingesta del laxante. **Resultados:** Las pruebas cutáneas a neuroalergenos ambientales (ácaros del polvo doméstico, epitelio de perro y gato) fueron positivas, así como las realizadas frente a extracto de *Plantago ovata*. La IgE específica (EIA y CAP-System) frente a *Plantago ovata* fue positiva y el SDS-PAGE Immunoblotting (Western blot) mostró bandas fijadoras de IgE de pesos moleculares 78, 59, 34, 25,6 y 17,6 kDa respectivamente. Una rinomanometría basal y una prueba de provocación nasal específico a *Plantago ovata* positivo. **Conclusiones:** La sensibilización a *Plantago ovata* es relativamente frecuente en trabajadores expuestos por vía inhalatoria (personal sanitario y de la industria farmacéutica). Existe un riesgo importante de reacciones graves anafilácticas tras su ingesta en individuos sensibilizados.

Palabras clave: Asma ocupacional. Anafilaxia. *Plantago ovata*.

The seeds of *Plantago ovata* (also known as *Psyllium* or *Ispaghula*) are used in the preparation of bulk laxatives. Since 1970 there have been a number of reports of respiratory allergic reactions following manipulation of the seeds. Pharmaceutical industry workers and health care personnel constitute the main risk groups for such reactions.

Up to the present date, nine cases of *Plantago ovata* anaphylaxis have been reported (Table I).

CLINICAL OBSERVATION

The patient was a 31-year-old male with no known toxic habits and with a personal history of surgically treated rhinosinusal polyposis. He is a pharmaceutical industry worker (Madaus Laboratories), who works at the weighing area in the raw materials storage zone. He usually manipulates *Plantago ovata* seeds for the preparation of the Plantaben® bulk laxative since 18 months prior to consultation.

He consulted because of episodes of rhinitis in association to dyspnoea, cough and wheezing since five months earlier, which were triggered by physical exertion, laughing, respiratory infections and in relation to his working time and to the manipulation of *Plantago ovata* seeds. He also reported one episode of facial angioedema, generalised urticaria, abdominal pain and bronchospasm after the ingestion of the laxative Plantaben®. The patient had carried out peak flow controls, evidencing peak flow falls in excess of 20% in the days when he manipulated the seeds and progressive improvement during the weekends. On the day of the ingestion of the laxative (and of the anaphylactic episode) he reported a 40% drop of his peak flow as compared to the maximum recorded levels.

METHODS

Skin tests: Skin tests were performed using the prick technique according to the EAACI recommendations with a panel of airborne allergens that are common in our environment. Prick tests were also carried out with a 1/100 w/v extract of *Plantago ovata* (Laboratorios Bial-Arístegui, Bilbao, Spain).

Specific IgE quantitation: This was carried out using the HY·TEC EIA technique with Ifidesa-Arístegui discs, using 2 mg/disc of allergen coupled to BrCN-activated pa-

per discs. The tests were developed with the commercially acquired equipment for the HY·TEC EIA test for specific IgE (Hycor Biomedical, Inc.). A second quantitation was carried out using the CAP·SYSTEM (Pharmacia, Uppsala, Sweden).

SDS-PAGE and SDS-PAGE Immunoblot: The discontinuous method described by Laemmli was used in 12.5% polyacrylamide gel; the protein bands were stained with Coomassie blue R-250 or with a silver stain as required, with parallel application of a molecular weight standard of proteins with known molecular weights (Pharmacia Biotech). Ten µl/lane of the standard or the sample were applied to each lane; the *Plantago ovata* protein contents were 20 µg (Bradford) when the Coomassie blue stain was used, and 1 µg when using the silver stain. The silver stain was performed with the Silver Stain Plus equipment of Bio-Rad, according to the manufacturer's instructions.

The proteins separated by the SDS-PAGE procedure were electrotransferred to PVDF membranes (Immobilon P®) and then incubated with the patient's serum. The IgE-binding bands were developed with an enzymatic system using 4-chloro-1-naphthol or luminol (chemoluminescence detection) as convenient. The molecular weight standard was developed with Amido Black.

Forced spirometry, bronchodilator test and specific nasal challenge test: A passive anterior rhinomanometry was performed at a time when the patient was asymptomatic; the *Plantago ovata* extract was then nebulised, initially at a 1:100,000 w/v dilution. Clinical and rhinomanometric controls were performed at 20-minute intervals, with progressive tenfold increases over the initial concentration.

RESULTS

Skin tests: The skin tests were positive for house dust mites and dog dander, as well as for the 1/100 w/v *Plantago ovata* extract. Similar skin tests were performed on ten atopic and ten non-atopic control subjects, with negative results in all cases. It was not possible to perform control tests to exposed workers from the same pharmaceutical company.

Specific serum IgE: The results were positive for *Plantago ovata* (19.22 IU/ml, Class 4) in the EIA quantitation (Bial-Arístegui), and again positive (4.7 IU/ml, Class 3) with the CAP·System. This system also yielded

Table I. Published cases of anaphylaxis caused by *Plantago ovata*

Case No.	Gender	Age (years)	Occupation	Ingested product	Respiratory symptoms	Authors
1	Female	33	Nurse	Laxative	No	Suhonen et al. ⁴ (1983)
2	Female	37	Nurse	Laxative	Yes	Zaloga et al. ⁵ (1984)
3	Female	35	Nurse	Cereal	No	Kaplan ⁸ (1990)
4	Female	39	Nurse	Laxative	Yes	Sussman and Dorian ⁶ (1990)
5	Female	42	Nurse	Laxative	Yes	Sussman and Dorian ⁶ (1990)
6	Female	60	Nurse	Cereal	No	Lantner et al. ⁷ (1990)
7	Female	38	Nurse	Cereal	No	Drake et al. ⁹ (1991)
8	Female	40	No	Laxative	No	Freeman ¹⁰ (1994)
9	Female	69	Nurse	Laxative	Yes	Vaswani et al. ¹¹ (1996)

positive results for *Dermatophagoides pteronyssinus* (Class 2) and dog dander (Class 3), and negative ones for *Plantago lanceolata* pollen.

SDS-PAGE Immunoblot (Western blot): IgE binding bands with molecular weights of 78, 59, 34, 25.6 and 17.6 kDa respectively were detected.

Forced spirometry: The spirometry confirmed nonspecific bronchial hyperreactivity and disclosed a mild obstructive respiratory disorder with positive bronchodilator test.

Specific nasal challenge test with Plantago ovata: the passive anterior rhinomanometry results revealed moderate obstruction at baseline. The specific nasal challenge test was positive at the 1/100 w/v concentration, with intense sneezing, rhinorrhoea, nasal pruritus, a 60% drop in the transnasal flow and an increase of the transnasal air-flow resistance.

Nasal challenge tests were also performed on five non-atopic control subjects with the *Plantago ovata* extract at a 1/1 w/v concentration, with negative results in all five cases.

DISCUSSION

The seeds of *Plantago ovata* (*Psyllium* or *Ispaghula*) are used in the preparation of bulk laxatives; a mucilage (soluble natural fibre with hydrophylic properties) is obtained from the cuticles of the seeds.

Since 1970, a number of cases of respiratory allergic reactions (both rhinoconjunctivitis and bronchial asthma) have been reported after the manipulation of the seeds. The main at-risk groups are pharmaceutical industry workers and health care personnel.

Several epidemiological studies of *Plantago ovata* sensitization in personnel at risk (health care personnel and pharmaceutical industry –laxatives– workers) have been published. The prevalence of sensitization among health care personnel varies depending on the criterion for positiveness being a positive prick test (5% prevalence) or a positive specific serum IgE (12% prevalence)¹. The prevalence is higher among pharmaceutical industry workers, respectively 19% and 26%². In Spain, Hinojosa *et al.*³ published four cases of occupational asthma among workers of a pharmaceutical laxatives company, with confirmation by skin tests, specific IgE and specific bronchial challenge tests.

Anaphylactic reactions have also been reported after the ingestion of *Plantago ovata* in laxatives and also after occult ingestion in cereals. Nine cases of reactions of this type have been published (Table I)⁴⁻¹¹. It is remarkable that all these patients were women and most of them were nurses, and that four of the nine cases had had respiratory symptoms prior to the anaphylactic episodes, in association to the manipulation of the cereal or the laxative. In Spain, only one case of anaphylaxis after ingestion of a *Plantago ovata*-containing laxative has be-

Table II. Results of the *Plantago ovata* sensitization study

Prick test <i>Plantago</i> 10 mg/ml (mm)	Specific IgE (CAP-System UI/l)	Specific IgE (EIA UI/l)	Total serum IgE (KU/l)	Specific nasal challenge test <i>Plantago ovata</i> 1mg/ml
4x4	4.7	19.22	109	Positive

en published, but without confirmation through allergic tests¹².

In 1989, following the introduction into the USA market of two *Psyllium*-containing cereals (Heartwise® and Benefit®), over 50 cases of reaction related to the ingestion of the former and 26 related to the latter were reported. A review of 20 of the 24 reactions related to the ingestion of Heartwise® and considered to be anaphylactic was published¹³. It is again remarkable that all those reactions occurred in women, 70% of them nurses, and that 73% of them had evidenced previous respiratory symptoms in relation to the manipulation of the material.

In 1984, Machado and Stålenheim¹⁴ reported a series of six patients who had developed respiratory symptoms (three of them rhinoconjunctivitis and three bronchial asthma) upon manipulating *Plantago ovata*. Oral challenge tests were carried out in all cases; all the patients developed respiratory (rhinitis) symptoms, three of them also digestive symptoms and cough, and two an urticariform rash.

The studies of the antigenicity of *Plantago ovata* seeds have revealed varying patterns of IgE-binding protein bands. Arlian *et al.*¹⁵ report multiple bands between 10 and 66 kDa in molecular weight that bound antibodies from the sera of eleven patients with respiratory symptoms and positive specific IgE (Class 2 to Class 5) to *Psyllium*. James *et al.*¹⁶ studied the sera of 20 patients with allergic manifestations after ingestion of *P. ovata* laxatives and found varying antibody-binding patterns: all the sera recognised 20- and 36-kDa bands, five cases recognised high-molecular-weight (66 and 60 kDa) bands, one case recognised low molecular weight (12 and 14 kDa) bands, and one case recognised all the reported bands. There is superposition between the various patterns; it would thus appear that there is no specificity of the antigenic pattern according to the sensitization and the clinical manifestations, either inhalatory or digestive.

In the case here reported, and besides the inhalatory sensitization and clinical manifestations, symptoms of anaphylaxis developed after the ingestion of the *Plantago ovata* laxative. The immunologic study has revealed IgE-binding protein bands of molecular weights similar to those already reported (59, 34, 25.6 and 17.6 kDa), and a

further previously not reported one with a molecular weight of 78 kDa.

REFERENCES

1. Malo JL, Cartier A, L'Archeveque J, Ghezze H, Lagier F, Tudeau C, et al. Prevalence of occupational asthma and immunologic sensitisation to psyllium among health personnel in chronic care hospitals. *Am Rev Respir Dis* 1990; 142: 1359-1366.
2. Bardy JD, Malo JL, Seguin P, Ghezze H, Desjardins J, Dolovich J, et al. Occupational asthma and IgE sensitisation in a pharmaceutical company processing psyllium. *Am Rev Respir Dis* 1987; 135: 1033-1038.
3. Hinojosa M, Dávila I, Zapata C, Cuesta J, Quirce S. Asma ocupacional inducido por polvo de semillas de *Plantago ovata* en trabajadores de la industria farmacéutica. *Rev Esp Alergol Inmunol Clin* 1990; 5: 139-145.
4. Suhonen R, Kantola I, Björkstén F. Anaphylactic shock due to ingestion of psyllium laxative. *Allergy* 1983; 38: 363-365.
5. Zaloga GP, Hierlwimmer UR, Engler RJ. Anaphylaxis following psyllium ingestion. *J Allergy Clin Immunol* 1984; 74: 79-80.
6. Sussman GL, Dorian W. Psyllium anaphylaxis. *Allergy Proc* 1990; 11: 241-242.
7. Lantner RR, Espiritu BR, Zumerchik P, Tobin MC. Anaphylaxis following ingestion of a psyllium-containing cereal. *JAMA* 1990; 264: 2534-2536.
8. Kaplan MJ. Anaphylactic reaction to "Heartwise". *N Engl J Med* 1990; 323: 1072-1073.
9. Drake CL, Moses ES, Tandberg D. Systemic anaphylaxis after ingestion of a psyllium containing breakfast cereal. *Am J Emerg Med* 1991; 9: 449-451.
10. Freeman GL. Psyllium hypersensitivity. *Ann Allergy* 1994; 73: 490-492.
11. Vaswani SK, Hamilton RG, Valentine MD, Adkinson NF Jr. Psyllium laxative-induced anaphylaxis, asthma and rhinitis. *Allergy* 1996; 51: 266-268.
12. Germán A, Aregall S, Boada L, Tomás S. Shock anafilático tras la ingestión de un laxante. *Med Clin (Barc)* 1995; 104: 559.
13. James JM, Cooke SK, Barnett A, Sampson HA. Anaphylactic reactions to a psyllium-containing cereal. *J Allergy Clin Immunol* 1991; 88: 402-408.
14. Machado L, Stålenheim G. Respiratory symptoms in isphagula-allergic nurses after oral challenge with isphagula suspension. *Allergy* 1984; 39: 65-68.
15. Arlian L, Vyzensky-Moher D, Lawrence AT, Schrotel K, Ritz H. Antigenic and allergenic analysis of Psyllium seed components. *J Allergy Clin Immunol* 1992; 89: 866-876.
16. James JM, Cooke SK, Barnett A, Sampson H. Anaphylactic reactions to a psyllium-containing cereal. *J Allergy Clin Immunol* 1991; 88: 402-408.