
Case report

Psyllium-associated anaphylaxis and death: a case report and review of the literature

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Background: Psyllium use has increased significantly in the United States in part due to its lipid-lowering property. The increased prevalence of consumption has led to its recognition as an emerging food allergen.

Objectives: To report the case of a 42-year-old woman who experienced fatal anaphylaxis after ingesting a psyllium-based product and to review the literature.

Methods: The MEDLINE database was searched for articles from 1966 to 2002 using the keywords *psyllium* or *ispaghula* and each of the following: *allergy*, *hypersensitivity*, *anaphylaxis*, and *asthma*. Both English and non-English articles were included.

Results: Psyllium hypersensitivity has been well described in health care workers and pharmaceutical plant employees. Clinical manifestations of allergy range from upper respiratory tract symptoms on inhalation to anaphylaxis on ingestion. The prevalence of sensitization varies between these 2 groups. The allergenic epitope is not known.

Conclusions: We present a case of psyllium hypersensitivity that resulted in death. There is a clear association between atopy and psyllium allergy. The case underscores the fact that even nonprescription “natural” products can be harmful to people with allergies.

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INTRODUCTION

Psyllium, or ispaghula, is a natural hydrophilic mucilloid of the genus *Plantago*. For years its hydrocolloidal property has made it a popular bulk laxative, and more recently studies have shown it to have a lipid-lowering property as well.¹ For these reasons, psyllium use has increased significantly in the United States in the last century. Given the increase in use, it is not surprising that adverse events are being reported more frequently. Psyllium is now being referred to as an emerging food allergen.^{2,3} Following Ascher's 1941 account describing the first reported case of psyllium hypersensitivity,⁴ case reports and epidemiologic studies describing psyllium-induced rhinitis, asthma, and anaphylaxis have been published. We report a case of psyllium-induced anaphylaxis that resulted in death. Our case significantly emphasizes the allergenicity of psyllium seed. To better understand psyllium hypersensitivity and prevalence of sensitization, the case report is followed by a concise review of the literature.

CASE REPORT

The patient was a 42-year-old woman with a history of asthma since childhood. Previous asthma history included frequent exacerbations that required tapering courses of prednisone. She was a nonsmoker. She worked as a certified nurses assistant in a rehabilitation and extended care facility,

where she was routinely exposed to psyllium while preparing the bulk laxative for patients. There were no documented previous adverse reactions. Her previous medical history was otherwise unremarkable and included peptic ulcer disease, cholecystectomy, and anxiety.

On August 30, 2000, the patient was brought to a local emergency department after experiencing acute respiratory arrest. As part of her new health program, the patient ingested a psyllium-based product called Clean Start (Nature's Sunshine Products Inc, Spanish Fork, UT), used for colonic cleansing. Within 5 minutes of taking her first dose, she began complaining of shortness of breath and throat swelling. She rapidly developed wheezing and respiratory arrest. An ambulance was called, and the patient was intubated and administered epinephrine, diphenhydramine, and methylprednisolone. Resuscitation efforts failed and the patient died.

Subsequent autopsy reported an elevated serum tryptase level of 15.7 ng/mL (reference range, 5.6–13.5 ng/mL). There was evidence of upper airway occlusion with severe laryngeal and epiglottic edema. Microscopy of the larynx and epiglottis demonstrated mucosal and submucosal edema. Giemsa staining of the laryngeal mucosa revealed focal degranulation of mast cells. Further serum evaluation showed high IgE antibodies to a number of allergens, including animal dander mix, mixed grass pollen, house dust mite, and tree pollen mix. The result of radioallergosorbent assay testing (RAST) to ispaghula was 4⁺ with a quotient of 1,862%. Postmortem serum samples were sent to the laboratories of Dr. John Yunginger at the Mayo Clinic, Rochester, MN, for

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Table 1. Serum IgE to 22 Ingredients of Clean Start Expressed as the Mean Percentage of Radioactive Counts Bound to Disk

Ingredient	Counts bound, %	
	Clean Start	Negative control
Licorice root	2.26	1.88
Burdock root	2.25	2.08
Yellowdock	2.45	2.00
Ginger root	2.00	1.86
Marshmallow root	2.18	1.89
Sarsaparilla root	2.29	2.99
Dandelion root	1.61	1.85
Red clover tops	1.78	1.34
Capsicum fruit	1.59	1.86
Oregon grape root	1.70	1.54
Turkey rhubarb	1.79	2.05
Fenugreek seed	2.19	2.00
Dog/couch grass herbs	1.77	1.77
Echinacea	3.04	3.99
Sterea extract*	1.56	2.01
Cascara sagrada bark	1.70	1.50
Buckthorn bark	1.60	1.37
Milk thistle concentrate	1.74	2.16
Sodium copper chlorophyllin	1.66	1.67
<i>Lactobacillus sporogenes</i>	1.74	1.57
Freeze-dried aloe vera*	1.52	1.90
Psyllium hull†	16.08	1.64

* Dissolved during extraction.

† Extracted 1:40 (wt/vol).

further analysis. The serum tryptase level was measured at 25 ng/mL, again substantiating the diagnosis of acute anaphylaxis. The results of in vitro assays for IgE specific antibody to 22 ingredients in Clean Start were negative except to psyllium (Table 1). Final cause of death was determined to be acute IgE-mediated anaphylaxis secondary to unrecognized occupational sensitization to psyllium in a highly atopic individual.

METHODS

At the Mayo Clinic, powder samples of each of the 22 individual ingredients in Clean Start were extracted 1:5 (wt/vol) in phosphate-buffered saline by mixing overnight at 4°C. All extracts were clarified by centrifugation and then coupled to cyanogen bromide-activated paper disks, which were then washed to remove unbound materials. Residual binding sites on the disks were blocked by incubation with assay diluent (100 mmol/L phosphate buffer containing 0.2% bovine serum albumin, 0.2% sodium azide, and 1% Tween 20). Coupled disks were used to test 2 serum samples, 1 postmortem sample from the patient and 1 from a nonallergic healthy person (negative control), in a radioimmunoassay for specific IgE antibodies.⁵

The MEDLINE database (1966–2002) was searched using the keywords *psyllium* or *ispaghula* and each of the following: *allergy*, *hypersensitivity*, *anaphylaxis*, and *asthma*. English and foreign language articles were included. The articles identified by this process were reviewed and included in

our review if there was any mention of psyllium and allergy in the title. Studies were excluded if they were reviews of the literature and did not present any patient information or original study results. References of included studies were reviewed looking for citations that meet criteria for inclusion but were not encountered during our initial search. If available, data for the following were extracted from case reports: exposure, symptoms, latency, sex, age, and confirmatory testing.

RESULTS

The initial MEDLINE search resulted in the identification of 570 studies, although some articles were cited more than once given the significant overlap in search keywords. Of these 570, 45 studies met the specified inclusion criteria. An additional 3 articles were identified through searching reference lists to yield a total of 48 included studies. Extracted data from case reports are presented in Table 2.

DISCUSSION

Psyllium allergy has been well described in health care workers^{6–14} and employees in pharmaceutical plants that manufacture psyllium.^{15–23} In fact, the disproportionately high incidence of psyllium hypersensitivity in these groups has led to the recognition that psyllium is a significant occupational allergen. Studies have concluded that these individuals are sensitized through occupational exposure.^{6–11,15–18,24} Manifestations of sensitization present as a spectrum of allergic illness, including rhinoconjunctivitis,^{9,10,13,23,27,49} asthma,^{6,7,9,11,12,15,19,28,47,48,50} granulomatous bronchiolitis,²⁹ eosinophilia,³⁰ and anaphylaxis.^{14,25,26,31–37,44–46}

Although inhaling psyllium usually results in rhinitis and bronchospasm, most cases of anaphylaxis usually occur after ingestion (as with our patient), presumably due to a much larger antigen load than could be inhaled. Machado and Stalenheim¹² demonstrated that nurses previously sensitized by inhalation experience upper airway symptoms 15 to 25 minutes after administration of an oral challenge. They theorized that ingested allergens caused systemic symptoms by first reacting in the intestinal wall and liberating cytokines into the circulation. A case-control study of atopic patients with allergy to psyllium showed that postantigen challenge of intestinal perfusate demonstrated elevated levels of albumin and hyaluronic acid in atopic patients only.³⁴ Increased levels of prostaglandin E₂ and eosinophilic cationic protein were found in atopic patients and controls. They concluded that the changes seen with intestinal challenge may or may not reflect early IgE-mediated effect and that more testing was necessary. The anaphylactic potential of oral psyllium in sensitized individuals was illustrated in the late 1980s with the introduction of 2 psyllium-containing cereals, which were later either withdrawn or reformulated due to case reports of anaphylaxis.³⁴ In a study of 20 women with allergy to Heart-wise cereal (Kellogg's, Battle Creek, MI), 14 were nurses.³⁴ This again suggests that those with allergy to ingested psyllium acquired their sensitivity by inhaling airborne psyllium.

Table 2. Reported Cases of Psyllium Allergy

Exposure	Asthma	Allergic rhinoconjunctivitis	Anaphylaxis	Latency	Sex	Age, y	Positive SPT result	Positive IVT result	Positive TlgE result	CCT	Reference
1 Pharmaceutical worker-inhalation		1/1		Unknown	M	27	1/1			Passive transfer	4
1 Nurse-inhalation	1/1	1/1		Seconds	F	26	1/1	1/1			7
5 Nurses-inhalation	5/5	5/5		1–4 min	4 F, 1 M	31–55	4/5	5/5		5/5 to IPC	9
2 Nurses-inhalation		2/2		Seconds	F	39, 39	1/2, not done in 1	1/2, not done in 1		Unknown test in 1/2	10
1 Nurse-inhalation	1/1			2 min	F	21					11
2 Nurses-inhalation	2/2	2/2		Unknown	F	33, 42	2/2	1/2, not done in 1		NPC in 1	13
2 Nurses-inhalation	2/2	2/2		Unknown	F	38, 40	2/2	2/2			14
1 Pharmaceutical worker-inhalation	1/1	1/1	2/2	45 min–6 h	F	52		1/1	1/1		15
1 Pharmaceutical worker-inhalation	1/1	1/1	1/1	Several months	M	28	1/1	1/1			18
3 Pharmaceutical workers-inhalation	3/3	2/3		<15 min	M	32, 32, 37	3/3			3/3 OPC	19
1 Husband-inhalation	1/1			5 mo	M	29	1/1			PK	24
1 Nurse-ingestion			1/1	30–60 min	F	60	1/1			BHR	25
2 Nurses-ingestion			2/2	30–60 min	F	39, 42	2/2	1/2, not done in 1			26
1 Nurse-inhalation	1/1	1/1		2 min	F	45		1/1	1/1	IPC	27
1 Nurse-inhalation	1/1	1/1		Symptoms for 10 y	F	45		1/1			28
1 Woman-inhalation	1/1			Few days	F	48					29
1 Patient-ingestion				6 wk	F	60				OPC	30
1 Nurse-ingestion			1/1	15 min	F	37	1/1	1/1	1/1	PK	31
1 Nurse-ingestion			1/1	Within 1 h	F	33	1/1	1/1	1/1		32
1 Nurse-ingestion			1/1	Minutes	F	48	1/1	1/1		PK	33
20 People-ingestion	17/20	11/20	>70%	2–30 min	F	27–73, ≥53		20/20			34
1 Nurse-ingestion			1/1	5–10 min	F	69	1/1	1/1	1/1	RAST inhibition	35
1 Nurse-ingestion			1/1	Minutes	F	43	1/1				36
1 Nurse-ingestion			1/1	25 min	F	38			1/1		37
3 Nurses-inhalation	2/3	3/3	1/3	seconds	2 F, 1 M	28, 33, 42	2/3, not done in 1				43
1 Patient-ingestion	1/1			15 min	M	47	1/1				44
1 Bank employee-ingestion			1/1	15 min	F	40		1/1	1/1		45
1 Patient-ingestion			1/1	4 h	M	54					46
1 Woman-inhalation		1/1		Unknown	F	31	1/1			IPC	47
1 Pharmaceutical worker-inhalation		1/1		Unknown	M	19					48
2 Nurses-inhalation		2/2		Unknown	F	39, 26	2/2			Unknown test	50

Abbreviations: BHR, basophil histamine response; CCT, confirmatory challenge testing; IPC, inhalational provocation challenge; IVT, in vitro testing; NPC, nasal provocation challenge; OPC, oral provocation challenge; PK, Prausnitz Kustner; RAST, radioallergosorbent assay test; SPT, skin prick test; TlgE, total IgE.

Anaphylaxis from an inhalation encounter is rare but has been described.¹⁴

Because occupational allergy has been mainly described in pharmaceutical and health care workers, a number of epidemiologic and cross-sectional studies have been conducted to determine prevalence rates of sensitization and occupational allergy. Some studies have been criticized because they based prevalence statistics on self-reported questionnaires. Well-designed studies have used challenge testing to confirm psyllium allergy. Prevalences of occupational asthma (OA) and sensitization are difficult to compare among studies because of divergent diagnostic criteria. For example, although OA was suspected in nurses handling psyllium, specific inhalational challenges with spirometry were not performed to confirm the diagnosis.⁸ When data are analyzed by occupational exposure, several studies are especially helpful. These studies report sensitization prevalence ranging from 7.6% to 25% among pharmaceutical workers.^{17,22,23} Bardy et al²¹ noted IgE sensitization by either RAST or skin prick test (SPT) in 32% of exposed pharmaceutical workers. OA was reported in 5 (3.6%) of 140 subjects after specific inhalational challenge. Interestingly, in a questionnaire survey, 39 of 130 subjects reported symptoms consistent with OA, but of those only 5 had positive inhalational challenge results.²¹ This speaks to the importance of objective testing and to the lack of sensitivity and specificity of questionnaires, which may reflect psyllium's potential irritant and not an allergic effect. In studying the prevalence of psyllium allergy in the health care industry, Nelson⁸ performed an epidemiologic investigation, surveying 743 health care workers in long-term care facilities, revealing 136 (18%) who experienced allergic symptoms on exposure. Five percent reported wheeze, shortness of breath, or hives. This study was criticized because no confirmatory testing was performed. Other researchers have investigated chronic care hospital personnel with questionnaires, SPT, RAST, or histamine or specific inhalational challenges and concluded the prevalence of IgE sensitization was 5% to 14.6% based on SPT or specific IgE, respectively,⁶ to as high as 25%.¹⁰ OA prevalence of 4% was confirmed by specific inhalational challenge.⁶

The role of IgE in psyllium hypersensitivity has been documented by SPT, RAST, and inhalational and oral challenges. It stands to reason that atopic individuals would be at greater risk for psyllium allergy than nonatopic individuals, and in fact this relationship is borne out in some studies.^{17,21,22,39} Unfortunately, few studies have reported on atopic status,^{6,9,13,23,34} whereas many studies and case reports failed to comment on the presence or absence of atopy. In many cases, the reader is left to infer atopy based on the SPT or RAST data.^{19,28,33} Kirby et al²² showed that of 47 sensitized pharmaceutical workers, 41 were atopic compared with 71 (52%) of 136 nonsensitized individuals. This was a statistically significant difference. Bardy et al²¹ also noted a significant association among atopy, IgE sensitization, and OA. They reported a 62% rate of atopy in his study population, with all 5 patients with OA being atopic. This study's higher

atopic rate may explain the higher prevalence of psyllium sensitization than other studies have found. McConnochie et al¹⁷ found a significant association between atopy and work-related symptoms and atopy and chest tightness (12 of 18 with OA were atopic). Conversely, Goransson and Michaelson¹⁶ reported no overrepresentation of atopic patients with ispaghula allergy among employees tested. Thus, the data are mixed; however, there are a number of case reports and cross-sectional studies that support a link between atopy and sensitization and atopy and OA.

There is much debate regarding the allergenic component of psyllium. It has been characterized as being a "gum" when electrophoresis of psyllium extract yielded no protein bands.⁴⁰ Arlian et al⁴¹ examined various *Plantago ovata* seed extracts by immunoelectrophoresis and microscopy and concluded that the allergenic component in psyllium products is derived from contaminating endosperm and embryo seed components rather than the husk itself. Lending credibility to this finding is the significant decrease in reports of allergy after the reformulation of Heartwise cereal in March 1990 to 95% pure psyllium.³⁴

Given the acceptance of an inhalational route as mode of sensitization, Machado et al²⁰ conducted a study that challenged 15 ispaghula allergic individuals with commercial grade and 3 other "less dust" formulations. They found the "lower dust" products resulted in a lower incidence of symptoms and concluded that lower dust preparations may reduce the potential for occupational sensitization. This indeed was the case in a pharmaceutical factory after it overhauled the manufacturing process to lower dust content.¹⁶ Nguyen et al⁴² undertook a study aimed at determining whether the total dose vs concentration vs duration of exposure to powdered high-molecular-weight agents was responsible for immediate allergic reactions. They concluded that the total dose, not concentration or duration, determined bronchial responsiveness. Although there is no uniform agreement on the allergenic epitope, it seems to be present in aerosolized particles, causing inhalational sensitization in a dose-dependent manner.

Diagnostic approaches include skin testing, in vitro testing, and provocation challenge. The key to any testing lies in the allergen preparation being used. Because standardized psyllium allergen is not available and reagents are variable, the literature in this area is difficult to summarize. Several studies have commented on what is the most appropriate testing tool when one suspects allergy to psyllium. Goransson and Michaelson¹⁶ found sensitization of 28 (44%) of 64 pharmaceutical employees by intracutaneous testing. The test results were positive in 18 of 27 who reported allergic symptoms and 10 of 37 without symptoms but with an exposure history. The test results were also positive in 6 of 60 controls. The group that had been exposed and subjectively symptomatic had a statistically significant increased frequency of positive reactions to skin testing. Bardy et al²¹ reported only 19% sensitization by SPT, much lower than what Goransson and Michaelson¹⁶ found. This was attributed to the decreased sensitivity of prick testing. A study of pharmaceutical work-

ers reports 5% sensitization by SPT and 10% by RAST, speaking to a greater sensitivity of RAST over prick testing, but presumably with more false-positive results as well.¹⁷ Other studies on prevalence of sensitization in nursing departments report SPT as more sensitive than RAST.¹⁰ Unfortunately, these studies did not comment on the definition of a positive or negative RAST result. Schwartz et al²⁷ report a case of a nurse with documented nasal obstruction to brief inhalational challenges to psyllium. They suggest that nasal airway challenge testing can be used in practice to evaluate treatment efficacy for occupational rhinitis. The literature validates the well-known fact that intradermal testing is more sensitive but less specific than SPTs. Studies conflict regarding the sensitivity of RAST vs SPT.

CONCLUSION

Review of the literature shows that inhaling psyllium in susceptible individuals may lead to symptoms of rhinoconjunctivitis and OA on subsequent airborne exposure and anaphylaxis on ingestion. This is presumably due to the large antigen load, but studies differ as to the exact mechanism of systemic effects. There is a higher prevalence of allergic sensitization in pharmaceutical companies than health care facilities. This may be due to higher antigen contamination in the plants that manufacture psyllium. Prevalence of OA on the other hand is similar. The data support an increased risk of sensitization or OA in atopic patients. The allergenic component of psyllium is not positively known, but studies indicate that aerosolized seed contaminants may be the culprit. Psyllium should no longer be considered an emerging food allergen; it is now firmly established as a potential life-threatening allergen. There are undoubtedly many people with risk factors for psyllium allergy. Those with unrecognized and undiagnosed psyllium sensitization are at particular risk for life-threatening anaphylaxis, even to nonprescription "natural" products.

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