Clinical and Experimental Allergy, 1990, Volume 20, pages 199–202

Ispaghula sensitization in workers manufacturing a bulk laxative

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Summary

Exposure to ispaghula dust in a pharmaceutical factory resulted in chest tightness/wheeze, nasal, and ocular or skin symptoms in 48 of 92 exposed workers. Whilst symptoms were not incapacitating in the majority (44) of these, one worker required antihistamines and three others experienced severe respiratory symptoms when exposed to the dust. These three were atopic, had a positive RAST and skin test to ispaghula; a combination unique to them. There was a significant relationship between work-related symptoms and atopic status, however, smoking did not influence symptoms, total serum IgE and specific anti-ispaghula IgE. We conclude that handling ispaghula produces an irritant effect in most exposed people, however, sensitization to the dust can occur with severe respiratory symptoms.

Clinical and Experimental Allergy, Vol. 20, pp. 199–202. Submitted 28 April 1989; revised 18 September 1989; accepted 2 October 1989.

Introduction

The husks and seeds of *Plantago ovata*, also known as ispaghula or psyllium, are hydrophilic, capable of absorbing up to forty times their own weight in water. When this occurs, they form a mucilagenous material which is an effective bulk laxative.

Inhalation of dust from pharmaceutical preparations manufactured from husks is known to cause symptoms in susceptible subjects, i.e. process workers [1–4], nurses, [2,5–8] or home users [9]. Specific sensitization to ispaghula has been shown by skin testing [1,4,6,8], anti-ispaghula IgE [4,6,8,10,11], and inhalation challenge [1,3,6,8,10], although not all sensitized subjects exhibit symptoms and likewise some non-sensitized subjects are affected [4]. Other factors have been considered to play a part in the disease process, e.g. smoking [11] and atopy [4,8]. Thus a factory processing ispaghula husks was studied with the aim of determining (1) the prevalence of symptoms relating to working with ispaghula, (2) the parameters of sensitization that may be used to define subjects with disease, and (3) the influence of smoking on specific and total IgE levels.

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Materials and methods

Seed husks imported from India are sterilized *en route* with ethylene oxide. Once the bacterial count is less than 1000/g the husks are sieved to remove large foreign bodies. Husks are then mixed with salt, coated with a sugar mixture and dried on a fluid air bed at 80°C. Further sieving removes larger aggregates before the powder is bagged. Dust is created in the packing area where the final product is dispensed into cartons.

Subjects

Manufacturing and processing in the factory is not a continuous operation and is largely dependent upon demand. When processing occurs, up to 13 workers are involved, three or four in the mixing room and between seven and nine in a separate dispensing/packaging room. The team varies in composition, being drawn from a pool of 80–90 workers who work together for 1 week, then, when required, another team is drawn from the same pool.

All current workers who had been exposed to the husks and final product were studied, along with two members of the administrative staff who had occasional contact. The nature of the operation means that each worker will have had a different pattern of exposure.

Clinical information

Questionnaire. All subjects completed the MRC Questionnaire on Respiratory Symptoms (1976) with additional questions of relevance to organic dust exposure concerning chest tightness, fever, chills, myalgia, nasal and ocular symptoms during or after exposure to the husks.

Skin tests and blood samples. All subjects were skin-prick tested with six common allergen extracts—house dust, house dust mite, tree pollen, grass pollen, cats' fur, *Aspergillus fumigatus* (Bencard Ltd, Brentford, U.K.)—and also with extracts of unprocessed ispaghula husk and the final product. A reaction (weal-and-flare) of 2 mm greater than the saline control at 15 min was taken as a positive result. At the same time, a sample of blood was taken and allowed to clot. Separated serum was stored at −70°C before use.

Occupational histories. These were obtained in full from all subjects.

Laboratory tests. Preparation of ispaghula extracts: the husks and final product were extracted, with a 1% phenol solution, overnight at room temperature. Insoluble material was discarded and the solution dialysed against running tap water. The dry weight per ml was determined and the concentration adjusted to 5 mg/ml by dilution, or by blowing air over the solution in dialysis tubing. The extract was made isotonic with 1/10 volume of × 10 saline and sterilized by filtration (< 0·22 μm Millipore).

Serological studies

IgE antibodies. Sera were tested for total IgE by the paper radioimmunosorbent test (PRIST) and for specific IgE antibodies to ispaghula by radio-allergosorbent assay (RAST) [12] using ispaghula-coated cellulose discs (Pharmacia Ltd, Uppsala, Sweden). A positive RAST was any serum which produced counts greater than the lowest concentration of reference anti-birch pollen serum/birch pollen-coated discs according to the manufacturer's instructions.

IgG antibodies. Specific IgG antibodies were determined by enzyme-linked immunosorbent assay (ELISA) using husk extract at 100 μg/ml in pH 9·6 carbonate–bicarbonate buffer (0·05 M) to coat Nunc-Immuno Plate (Gibco Ltd, Renfrewshire, U.K.) wells (overnight 4°C). Human sera were diluted to 1/500 in PBS (pH 7·2) and alkaline phosphatase-conjugated anti-human IgG (Miles-Yeda Ltd, Bethesda, U.S.A.) was used at 1/1000. Bound phosphatase was assayed using *p*-nitrophenyl phosphate (Sigma, Poole, U.K.) at 1 g/l in 10% diethanolamine pH 9·8.

Precipitin antibodies were determined by gel diffusion against husk and product extracts at 1 and 5 mg/ml.

The same extracts were used for ELISA assays, gel diffusion and skin-prick tests.

Results

Clinical and serological findings

Ninety-two employees were interviewed and tested, 21 were male with an age range of 22–62 yr (mean 40·6 ± 11·7 yr); the 71 females had an age range of 19–56 yr (mean 40·9 ± 9·5 yr). Work-related symptoms, i.e. symptoms experienced during the handling of ispaghula, were admitted by 48 (52%) and of these, 18 (20%) described chest tightness/wheeze (Table 1). Three employees reported severe respiratory symptoms when exposed to ispaghula, i.e. they could no longer go near the room where the husks were processed. One also reported wheezing throughout the night following skin-prick testing. A fourth employee who still handled the product required oral antihistamine to keep her work-related symptoms under control. The remainder tolerated their symptoms and the widespread use of masks provided a degree of control.

Thirty-six employees (39%) had a positive immediate skin-prick test to one or more common allergens (Table 2). Five (5%) had positive skin-prick tests to ispaghula of whom three were positive to both husk and final product and two were positive to husk alone. No late skin reactions were noted. Twenty normal controls with no exposure to ispaghula had negative skin-prick tests to both extracts. Sixteen subjects had elevated IgE levels (greater than 80 kU/l), seven had levels greater than 250 kU/l. Nine employees had a positive RAST ispaghula, two of these had total IgE greater than 80 kU/l.

Table 1. Symptoms experienced by workers in response to ispaghula exposure. Some workers had more than one symptom

Symptom	Number of workers affected
Chest tightness and/or wheeze	18
Sneeze	4
Nasal symptoms (stuffiness or discharge)	27
Gritty eyes	24
Itchy skin	1
No symptoms	44

Table 2. Relationship between work-related symptoms, atopicity, sensitization and smoking

		Ispaghula		Smoking		
	Number atopic	RAST	ST	NS	S	EX
Total workforce ($n=92$)						
All work-related symptoms ($n=48$)	24	5	4	22	23	3
No symptoms ($n=44$)	12	4	1	22	14	8
Chest tightness/wheeze ($n=18$)	12	4	4	8	8	2
No chest tightness/wheeze ($n=74$)	24	5	1	36	29	9

Atopic, skin-prick test positive to one or more common allergens; RAST, positive RAST to ispaghula; ST, positive skin-prick test to ispaghula (husks and/or final product); NS, non-smokers; S, current smokers; and EX, ex-smokers.

The relationship between (1) all work-related symptoms, (2) workers with chest tightness/wheeze and skin test reactivity to common allergens and ispaghula, and to ispaghula RAST testing is shown in Table 2. Significant relationships (chi-square test) were observed between atopy and work-related symptoms ($P<0{\cdot}05$) and also between atopy and chest tightness/wheeze ($P<0{\cdot}01$). The three most severely affected subjects were atopic, RAST and skin-test positive to ispaghula. Their respiratory response to the dust, which was typical of asthma though not demonstrated as such with reversibility tests, prevented them from working in the environment. A fourth subject, moderately affected, was able to control the situation with antihistamines and was atopic and RAST positive to ispaghula.

Low levels of IgG antibody to ispaghula were detected in seven workers. An ELISA reading of more than two standard deviations greater than the mean value for the workforce as a whole was considered positive. There was no correlation between sensitivity to ispaghula and elevated IgG to ispaghula. No precipitating antibody was detected by double-gel diffusion.

Smoking and symptoms

Thirty-seven workers (40%) were current smokers and 11 (12%) were ex-smokers. No relationship was observed between work-related symptoms (as a whole or as the chest tightness/wheeze group) and smoking status either including ex-smokers with current smokers or non-smokers, or omitting the group. Likewise, no relationship between smoking and IgE levels or specific anti-ispaghula IgE levels was observed either using data *per se* or with logarithmically transformed data. Arithmetical means for serum IgE levels (in kU/l) were: non-smokers 65 ± 156, smokers 103 ± 167, and ex-smokers $19\pm8{\cdot}5$. Geometric means (as antilog in kU/l) were: non-smokers $24\pm3{\cdot}5$, smokers $40{\cdot}7\pm4$, and ex-smokers $16{\cdot}4\pm1{\cdot}8$. Five workers with anti-ispaghula IgE were non-smokers, three were smokers and one an ex-smoker.

Dust measurements

It was considered impractical to undertake dust measurement because of (1) the intermittent nature of exposure, (2) the obvious exposure differences with visible dust at filling point compared with other parts of the production line, (3) the remedial measures, e.g. extraction fans, and (4) the masks available and worn by most of the workforce. However, for workers with symptoms estimated, cumulated dust exposure was $10\pm2{\cdot}3$ years compared with $7{\cdot}1\pm4{\cdot}2$ yr for workers not experiencing symptoms. For the group with chest tightness/wheeze, exposure was similar to the latter group.

Discussion

Occupational asthma is well-documented with causative agents as diverse in chemical and physical form as platinum salts, [13] toluene di-isocyanate, [14] rat urine, [15] egg protein [16], etc. Difficulties experienced in clinical diagnosis and establishment of the causative agent may be overcome by inhalation challenge with the putative agent. However, for ispaghula great caution should be exercised [8] and we did not consider it ethically acceptable, particularly in view of successful diagnosis achieved by Kirby *et al.* [4] using less traumatic procedures, i.e. clinical history, RAST and skin testing.

Our results confirm previous work of symptoms, i.e. asthma/rhinoconjunctivitis, correlating wtih atopy, positive RAST and skin testing to ispaghula [4,8], although our overall prevalence of specific (IgE and/or skin test)

positivity to ispaghula was 11/92 (12%) compared with 47/188 (25%) [4] and 9/60 (15% RAST only) [11] in other studies.

We could not relate increased anti-ispaghula IgE to smoking habits, in contrast to the findings of Zetterstrom *et al.* [11]; 3/9 RAST positives in our study were current smokers compared with 8/9 in the study of Zetterstrom *et al.* of 60 workers. Neither did smoking significantly affect serum IgE levels, although the means for smokers were higher than for non- and ex-smokers.

In our study only the three (3%) most severely affected workers were atopic with positive RAST and skin test to ispaghula compared with 14/188 (7·5%) in Kirby *et al.*'s study [4], although no data on response severity was reported. A further three workers had been unable to participate in ispaghula handling due to severe reactions and had left the factory (for other reasons). This suggests that the prevalence rate for severe responses to ispaghula at 3% could be an underestimate. The prevalence of all work-related symptoms (52%) and other published prevalence rates, i.e. 36% [11], 42% [2] but lower sensitization rates suggests that ispaghula has an irritant action. However, specific sensitization may occur, leading to severe IgE-mediated reactions with inhaled [8] or ingested ispaghula [7]. Wearing of masks and other remedial measures, e.g. production of larger ispaghula granules [3], minimizes respirable dust and allows most workers to continue at their workplace.

In view of the ability of this laxative to induce more than its desired pharmaceutical effect when ingested by sensitized subjects [7] it is suggested that subjects exposed by the respiratory route, e.g. nurses and pharmaceutical workers, consider some other laxative should they require such medication.

Acknowledgments

The authors wish to thank both management and staff of the firm where this study was performed. We would also like to thank Dr R. Jacobs, formerly of the Employment Medical Advisory Service, Cardiff, who brought this problem to our attention.

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