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Pickled onion–induced asthma: a model of sulfite-sensitive asthma?

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Summary

Background Asthma elicited by sulfite ingestion has been mainly described in steroid-dependent and in non-atopic asthmatics. We have studied a group of 18 young extrinsic asthmatics who presented with asthma attacks immediately after eating pickled onions.
Objective The aim of this study is to ascertain if these asthma attacks are elicited by sulfites contained in pickled onions and the influence of the dose and pH of onions.
Methods The bronchial hyperreactivity of the patients was assessed by a methacholine challenge test. Oral challenge tests were performed with sodium metabisulfite (MBS) diluted in lemon juice at pH 4·2 and at pH 3·3 (only in patients who did not react with pH 4·2). Two types of pickled onion, Spanish and Dutch pickled onions, were used for oral challenge in seven of the patients. The Monier–Williams method was used to measure the SO_2 concentration in pickled onions.
Results The oral provocation test with MBS, pH 4·2, elicited a positive response in six patients (33·3%) and the test at pH 3·3 was positive in three out of 12. No significant difference in PD20 values was found between these groups. Three of the seven patients challenged with Spanish pickled onions had a positive reaction but had no reaction with Dutch pickled onions. The SO_2 concentration in Spanish pickled onions varied between 765 and 1182 ppm while in Dutch pickled onions were 200 ppm; this exceeded the permitted level (100 ppm). SO_2 release in Spanish pickled onion samples was nearly 2·5 times higher when the pH of the sample decreased from 4·2 to 3·3.
Conclusion High levels of SO_2 in Spanish pickled onions, and their low pH (3·3) would be the responsible factors of the asthmatic outbreaks after ingestion of Spanish pickled onions by these patients.

Keywords: asthma, bronchial provocation tests, bronchial hyperreactivity, sulfites, sulfur dioxide, food preservatives, food analysis

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Introduction

Sulfites have antioxidant properties due to their capacity of eliciting sulfur dioxide (SO_2) and are commonly used as preservatives in the processing and storage of foods and beverages. Sulfiting agents prevent browning and microbial growth, they modify the texture of certain types of flour dough and bleach certain foods, such as pickled onions. They are also used as antioxidants by the pharmaceutical industry.

SO_2 and five sulfite salts listed in the code of American Federal (FDA) regulations have been generally recognized as safe, but current FDA regulations require that the labels of any packaged food with more than 10 ppm SO_2 must list sulfites or SO_2 as an ingredient [1]. Spanish regulations [2] control the concentration of sulfiting agents in foods and beverages: sulfur dioxide (E 220),

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sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium bisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228).

There are numerous reports about bronchospasms triggered in patients with asthma after ingesting foods containing sulfites [3–5]. The mechanisms through which ingested sulfites induce bronchospasm have not been fully established. The most currently accepted are the stimulation of tracheobronchial receptors by SO_2 and the induction of a cholinergic reflex [6], an IgE-mediated mechanism [7,8] and a partial deficiency of sulfite oxidase enzyme [1,9].

Asthma elicited by sulfite ingestion was first described between steroid-dependent asthmatics [10] and in non-atopic asthmatics with chronic vasomotor-type rhinosinusitis [11]. A high prevalence of sensitivity to sulfites has been shown by Towns [12] and Friedman [13] in children with asthma. More recently, Boner *et al.* [14] were unable to confirm this high prevalence in a population of children with mild chronic asthma. Bearing in mind the existing relationship between sensitivity to sulfites and the grade of bronchial hyperreactivity [14], a more severe asthma in populations studied by Towns and Friedman could be a reason for the discrepancy between the differences in the prevalences.

We present a peculiar group of young asthmatic patients who presented asthma attacks immediately after eating pickled onions, a food that is usually consumed by young people and bought by weight (not bottled). The aim of this study was to ascertain if these asthma attacks were elicited by sulfites contained in pickled onions. The possible influence of the dose and pH of onions and the degree of non-specific bronchial hyperresponsiveness in the bronchospastic responses was also investigated.

Patients and methods

Subjects

Eighteen patients (10 males and eight females), ranging in age from 12 to 23 years (mean 16·3 years) participated in the study. Patients' characteristics are shown in Table 1.

All the patients suffered from extrinsic mild–moderate asthma, as defined by the American Thoracic Society [15]. In all but two patients, was it possible to demonstrate hypersensitivity to *Dermatophagoides pteronyssinus* based on positive clinical history, skin test and RAST. The other two patients were allergic to *Alternaria* and rye grass pollen, respectively. Only three patients were treated with inhaled steroids and the remaining were on treatment with inhaled β2-agonists PRN (only as a rescue medication).

All patients had suffered, in the last 2 years, one or more asthmatic attacks immediately (<1 min) after ingestion of only one pickled onion, while most of them did not react to salads, vinegar, fruit juices, beer, cider, grape juice, shellfish and several pickled vegetables, including small Dutch pickled onions. Only one patient suffered an asthma attack after ingesting pickles (patient 7). They all eat raw and cooked onion regularly without showing any oropharyngeal symptoms.

Two different types of pickled onions bought by weight (unbottled) are commonly consumed among Spaniards: Spanish pickled onions that weigh around 20 g, and smaller Dutch pickled onions, whose weight is approximately 5 g. The pH of both onions is 3·3 and the two are preserved with the same solution. Spanish pickled onions were responsible for the asthmatic outbreaks in all our patients.

Before challenge tests with sulfites, skin-prick tests (SPT) were performed with a solution of sodium metabisulfite (MBS) 10 mg/mL and the preserving liquid of pickled onions. A 'prick by prick' test was done with raw and pickled onions. Histamine chloride (10 mg/mL) and saline solutions were tested as positive and negative controls. As all patients eat raw and cooked onion regularly without any trouble, a challenge test with raw onion was not considered. Levels of sulfite oxidase were not studied.

The study was performed on three consecutive days, when asthma was stable and FEV_1 had to be at least 1.5 L as well as 70% of their best prior value. β2-agonists were stopped at least 72 h before the test, while inhaled steroids were maintained. Pulmonary function studies were performed with a micro-22 spirometer (Schatzman, Madrid, Spain). The best of three FEV_1 values was chosen.

On the first day, PD20 was determined by methacholine inhalation. On the second and third day, oral challenges with sulfites diluted in lemon juice at two different pH were carried out.

Methacholine challenge

After five inhalations of buffer solution, and only if the change in FEV_1 was <10%, the patients took five deep inhalations with each of the Provocholine® (Roche, Basel, Swizerland) concentrations administrated with a respirator Mark 8 (Bird, Palm Springs, USA) following Towley's recommendations [16]. The responses were classified according to the PD20 as severe (<25), moderate (25–125) and mild (>125).

Table 1. Characteristic of patients and results of challenge tests with metacholine (PD20 in BU) and MBS (doses [mg] and FEV_1 drop in %) at pH 4·2 and pH 3·3, and pickled onions

n	Age & sex	FEV_1 %Prior	PD20	MBS pH 4·2	MBS pH 3·3	Pickled onions
1*	16M	100	11	75 (20%)	NT	54%
2	16F	109	64	Neg	Neg	NT
3*	14F	117	28	150 (25%)	NT	NT
4	14F	93	12	Neg	Neg	Neg
5	17F	81	NT	Neg	Neg	Neg
6	16F	93	45	100 (25%)	NT	20%
7	19M	93	37	Neg	75 (20%)	29%
8	13M	86	98	Neg	Neg	Neg
9	12M	85	Neg	Neg	Neg	Neg
10	20M	125	23	Neg	Neg	NT
11	18F	94	12	Neg	100 (25%)	NT
12	19M	105	14	Neg	150 (22%)	NT
13	13F	91	10	150 (51%)	NT	NT
14	15M	80	5	Neg	Neg	NT
15	13M	87	20	100 (42%)	NT	NT
16*	18M	89	125	Neg	150 (24%)	NT
17	23M	80	27	100 (20%)	NT	NT
18	19F	83	30	Neg	Neg	NT

F. Female. M. Male. BU. Breath unit. NT. Not-tested. Neg. Negative. * Patients treated with inhaled steroids.

MBS challenge test

A single-blind challenge test following the recommendations of Stevenson and Simon [11] and Prieto [17] was performed. Doses of 1, 10, 25, 50, 75, 100 and 150 mg of MBS (Sigma, St Louis, USA) diluted in 15 mL of lemon juice at pH 4·2 (adjusted by natrium hydroxide addition), were given to the patients at 10 min intervals. The solution was made just before the ingestion and the patients swished the solution in their mouths for at least 20 s before swallowing.

MBS challenge was not done if the variability in basal FEV_1 was >5%. The spirometry was carried out at 3 and 10 min, or sooner if symptoms occurred. The test was considered positive when at least a 20% drop in FEV_1 from baseline was measured after MBS administration. Positive challenges are easily reversed by inhaling 200 μg of Salbutamol (MDI) meteor doses-fixed inhalator.

To study the influence of pH changes on the elicitation of asthma, only in cases of negative MBS challenge test with lemon juice at pH 4·2, the test was repeated the next day with the same doses but with lemon juice at pH 3·3, which is the pH found when studying different samples of pickled onions.

Pickled onion challenge test

Seven patients consented to undergo this test. Twenty grams of two different types of pickled onions, Spanish and Dutch, at pH 3·3, were given on two separate days and the same criteria for challenge test with MBS were required. FEV_1 measurements were done, 3, 10 and 15 min after the ingestion and a decrease of 20% or more was considered a positive response.

Sulfite analysis

Since the histories suggested that the attacks of asthma were due to the sulfites contained in pickled onions, we performed an analysis following the Monier–Williams' method [18]. This procedure measures total sulfurous acid (free sulfites plus some bound forms of sulfite) expressed as SO_2 equivalents. SO_2 was released when the sample was submitted to heat and pH 1. The SO_2 is drawn over by a nitrogen current for 25 min; SO_2 changes to sulfate acid in the presence of hydrogen peroxide with red methyl and the neutralization takes place just at the toning-point. Then the assessment is done by alkalinization with natrium hydroxide 0·1 N.

The sulfite analysis were performed on Spanish and Dutch pickled onions, bottled pickled onions, their preserving liquids, raw onions, pickles and the solutions of MBS in lemon juice used in the challenge test. The SO_2 elicitation from Spanish pickled onions was measured at

Table 2. SO_2 concentration (ppm) in several types of pickled onions, raw onion and pickles

	Preserving liquid	Food
Spanish PO	155–660	765–1182
Dutch PO	180	200
Bottled PO	43–80	50–200
Onion		27–47
Pickled	5	50

PO. Pickled onions.

three different pH values: 1, 3·3 and 4·2. All measurements were performed three times.

Statistical analysis

Mann–Whitney test was employed (with Epi Info version 5.01 a statistical analysis program) to determine whether the differences of PD20 mean among patients with positive or negative MBS challenge test was significant.

Informed consent was obtained from each patient or both parents and the protocol was approved by the hospital's ethics committee.

Results

Skin-prick tests with MBS, pickled onions, the preserving liquid and raw onions were negative in all patients. Table 1 shows the results of challenge tests PD20 methacholine was negative in patient number 9 (MBS and pickled onion challenge test were negative too), mild in patient number 16, and moderate in seven and severe in eight of the patients.

Six patients (33·3%) had a positive response when the MBS challenge test was performed with MBS solution at pH 4·2 (one with 75 mg, three with 100 mg and two with 150 mg). However, four (22·2% of the total) of the 12 patients with negative reaction after MBS challenge at pH 4·2 presented a positive response with MBS at pH 3·3. The doses causing a positive response in these patients were: one 75 mg one 100 mg and two 150 mg.

All patients with positive reaction at pH 4·2 had mild to severe hyperreactivity to methacholine (PD20, mean 23·67 BU). No significant difference in PD20 methacholine values was found among the six patients with positive MBS challenge test at pH 4·2 (PD20 mean 23·67 BU) and the patients with negative reaction at pH 4·2 (PD20 mean 42·10 BU).

A positive reaction within 3 min after eating 20 g of Spanish pickled onions was observed in three of the seven patients challenged. These three patients had a positive MBS challenge test, two at pH 4·2 and the other at pH 3·3 though they tolerated 20 g of Dutch pickled onions with lower content of sulfites. None of the four patients who tolerated both types of pickle onions had a positive challenge test with MBS.

The SO_2 concentration in foods is shown in Table 2. Spanish pickled onions that elicited asthma in our patients presented a maximal level of SO_2 between 765 and 1182 ppm while the level on Dutch pickled onions was 200 ppm. Both types of pickled onion and the preserving solution (155–660 ppm) highly exceeded the permitted levels (100 ppm). Bottled pickled onions presented lower levels than those not bottled. Raw onions elicited 27–47 ppm of SO_2 quantity, similar to pickled ones.

The results of the total content of SO_2 in Spanish pickled onions at three different pH according to Monier-Williams are as follows: SO_2 at pH = 1, 626 ± 13; SO_2 at pH = 3·3, 496 ± 22; SO_2 at pH = 4·2, 209 ± 55. When the pH value decreased from 4·2 to 3·3 the SO_2 release rose nearly 2·5 times. Similar results were obtained with lemon juice: 2·5 times more SO_2 was elicited at pH 3·3 than at pH 4·2.

Discussion

We studied 18 young (12–23 years) patients with mild–moderate extrinsic asthma. They presented asthma attacks after eating pickled onions, a foodstuff containing a great quantity of sulfites. The inhalation of SO_2 is the suspected mechanism.

The profile of these patients is very different from that described for sulfite-sensitive asthmatics: chronic asthma and usually steroid dependent [10] and non-atopic asthma with chronic vasomotor-type rhinosinusitis [11]. In none of our patients asthma was intiated after a pickled onions reaction. Little medication was required and stable condition was present in most of them. Our asthmatics had features more similar to children studied by Boner [14] whose sulfite-sensitivity was related with a high reactivity to methacholine.

We think that the main cause of asthmatic attacks, in our patients, was the extremely high quantity of sulfites contained in unbottled pickled onions (765–1182 ppm). A pickled onion of 20 g of weight contains around 30 mg of MBS. The three patients with positive challenge test with 20 g of Spanish pickled onion (765–1183 ppm) tolerated 20 g of Dutch pickled onion (200 ppm). Doses of MBS lower than 75 mg did not elicit reaction and doses of 75 mg were required to elicit reaction in two patients, 100 in four and 150 in the remaining four.

In the USA it has been estimated that the average consumption of sulfites in home-prepared meals can be

up to approximately 10 mg/day and that restaurant meals can contain 100 to 400 mg. The foods that contain high levels of sulfites are dried fruit (1000–3000 ppm) and instant potatoes (50–100 ppm) and a single 85 g dinner salad size portion of lettuce prepared with a commercially available sulfite 'freshener' contains approximately 100 mg of sulfite [11].

Howland and Simon [19] reported five sulfite-sensitive asthmatic individuals who reacted to sulfite treated lettuce; none reacted to the non-sulfite-containing lettuce. In contrast, food with smaller amounts of mostly bound sulfite (shrimp and potatoes) did not provoke reactions [11].

Another important factor is the low pH (3·3) of pickled onions that with the warm environment of the mouth facilitates the SO_2 release as has been reported previously [20,21]. The sulfite analysis demonstrated that the decrease of pH from 4·2 to 3·3 enhances the SO_2 release 2.5 times. Moreover, four of the 12 patients who did not react with MBS at pH 4.2 had a positive response with MBS at pH 3·3. However, Prieto [22] did not find differences in MBS challenge test at pH 4 and pH 2·2–2·6.

In spite of the negative response to the challenge test with pickled onions in four of the seven patients tested, it is suggestive that pickled onions have special conditions responsible for the asthmatic outbreaks. One unbottled pickled onion that weighs 20 g and contains approximately 30 mg of sulfites produced an FEV_1 drop of 29% in patient 7 who tolerated the ingestion of 150 mg of MBS solution at pH 4·2. In patient 1, the pickled onion challenge test elicited a 54% fall of FEV_1 while the drop with 75 mg of MBS, at pH 4·2, was 20%.

Besides the influence of a low pH and the mouth temperature, the rough way the pickled onions were masticated by our patients (as observed during the challenge test) could induce an extremely sudden release of volatilized SO_2 from the free and bound sulfites of this food. Apart from the sulfites that are naturally in onions (27–47 ppm according to our measurements) some sulfites added to the preserving solution can be bound in dissociable combined forms with some constituents of pickled onions and can be released promptly during the mastication.

It is well established that the asthmatic reaction elicited by sulfites can depend on negligible factors, as the ingestion in capsules or in solution [20,23]. In our cases the circumstances of mastication seem to be important in asthma elicitation and can explain that, while a relatively low quantity of sulfites contained in pickled onions produced a positive challenge test, larger quantities in MBS solution were unable to produce it.

The lack of reaction to pickled onions challenge in four patients could be due to variations in bronchial hyperreactivity. The only patient who had asthma after eating pickles had a PD20 of 37 BU and a positive MBS challenge test at pH 3·3. The three patients treated with inhaled steroids had a positive MBS challenge test (two at pH 4·2 and the other with pH 3·3).

Although the mean of PD20 in the six patients with positive MBS challenge test at pH 4·2 was nearly twofold lower than among non-reactors at this pH, the difference was not statistically significant. In fact, sulfite-sensitive asthmatic individuals do not have heightened cholinergic sensitivity to SO_2 when compared with non-sulfite sensitive asthmatic individuals [5,24–26]. However, Boner [14] reported a significant correlation between methacholine challenge (PC20 and MBS challenge (200 mg) in children. In our study, the patients did not exactly remember the circumstances of their episodes because, in the majority of the cases, many months had passed by. Almost all the patients had, at some time of their evolution, been treated with inhaled corticoids, as well as with cromones and immunotherapy. It is possible that the treatment prescribed may have modified the evolution of their asthma and perhaps because of this, eight patients did not respond positively to the sulfites. Anyhow, the large amount of SO_2 generated by pickled onions may simply be confirming the non-specific bronchial hyperreactivity characteristic of the asthmatic population. Although the outbreaks of asthma presented by our patients were mild and easily reversed, there exists a risk of severe reactions with foods, such as pickled onions, containing sulfite levels above legal regulations.

While no correlation between the positive MBS challenge test and the degree of bronchial hyperreactivity was observed in our patients, we conclude that the high doses of sulfites contained in pickled onions, the low pH of this food and the way of the ingestion would be the responsible factors of a peculiar group of sulfite-sensitive asthmatics.

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