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Sensitivity to Sulfited Foods among Sulfite-Sensitive Subjects with Asthma

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Abstract

Eight individuals with asthma who had been diagnosed as sulfite sensitive on the basis of double-blind capsule-beverage challenges were subjected to challenges with various sulfited foods, including lettuce, shrimp, dried apricots, white grape juice, dehydrated potatoes (as mashed potatoes), and mushrooms. Four of these patients failed to respond to challenges with any of the sulfited foods. The other four patients experienced a decrease in pulmonary function on double-blind challenges with sulfited lettuce. Two of three of these patients reacted to challenges with dried apricots and white grape juice; the fourth patient has not yet been challenged with these products. Only one of these four patients reacted to challenges with dehydrated potatoes and mushrooms, and, in this case, the response to double-blind challenges with dehydrated potatoes was not consistent. None of the sulfite-sensitive subjects with asthma responded to challenges with sulfited shrimp. It is concluded that sulfite-sensitive subjects with asthma will not necessarily react after ingestion of sulfited foods. The

likelihood of a reaction is dependent on the nature of the food, the level of residual sulfite, the sensitivity of the patient, and perhaps on the form of residual sulfite and the mechanism of the sulfite-induced reaction.

Abbreviations used
FDA: Food and Drug Administration
SO_2: Sulfur dioxide
$K_2S_2O_5$: Potassium metabisulfite

A variety of sulfiting agents, including SO_2, sodium and potassium bisulfite, sodium and potassium metabisulfite, and sodium sulfite, are widely used as food ingredients.[1] Sulfiting agents prevent browning, control microbial growth and spoilage, modify the texture of certain types of flour doughs, and bleach certain foods, such as maraschino cherries.[1] The FDA considers these sulfiting agents to be generally recognized as safe for all food uses except their use on fresh fruits and vegetables, other than potatoes, intended for consumption in the raw state. Recently, the FDA has modified the status of sulfites as food ingredients by rescinding its generally recognized as safe status for use on raw fruits and vegetables and has required that the presence of sulfites be declared on the label of packaged foods when residue levels exceeded 10 ppm of sulfite expressed as total SO_2.[2,3]

The recent restrictions on the use and labeling of sulfites stem from concerns regarding the potential of these compounds to initiate adverse reactions in sensitive individuals. Although sulfites are apparently safe for consumption by most subjects,[4] numerous studies have described individuals with sulfite sensitivity who experience adverse reactions on ingestion of sulfiting agents.[5–10] The most common complaint is asthma,[5–10] although other types of adverse reactions have been reported occasionally.[8] Sulfite-induced asthma is most likely to affect steroid-dependent subjects with asthma.[7] The overall prevalence of sulfite sensitivity among subjects with asthma is estimated at 3.9%,[7] whereas the prevalence among steroid-dependent subjects with asthma is estimated at 8.4%.[7]

The preferred method for the diagnosis of sulfite sensitivity is a double-blind challenge test with capsules and/or acidic beverages containing one of the sulfite salts, usually $K_2S_2O_5$.[5,8] This challenge test determines whether an individual will react to oral ingestion of free, inorganic sulfite. However, when sulfiting agents are added to foods, they often react with other food components, forming a variety of bound forms of sulfite.[1] The responsiveness of sulfite-sensitive subjects with asthma to these bound forms of sulfite has not been demonstrated. The objective of this study was to evaluate the response of sulfite-sensitive subjects with asthma to challenges with a variety of sulfited foods.

Material and Methods

Subjects

Eight sulfite-sensitive subjects with asthma, including six with steroid-dependency, were identified with a combination of single-blind and double-blind challenges with capsules and neutral beverages containing $K_2S_2O_5$, as described earlier,[7] or single-blind challenges with acidic beverages containing 0 to 100 mg of sodium metabisulfite. The characteristics

of these patients and their response to sulfites are detailed in Table I. Six of these sulfite-sensitive subjects with asthma were identified by the screening of more than 200 subjects with asthma with double-blind capsule-beverage challenges.[7] The other two patients in Table I were identified by further evaluation of 12 possibly sulfite-sensitive subjects with asthma who originally had positive single-blind challenges to sulfite in acidic beverages. All eight of these subjects had histories consistent with sulfite sensitivity, although the histories of patients 6 and 7 were not especially convincing. In this study, steroid-dependent subjects with asthma were defined as those requiring either oral (daily or alternate day) or daily inhaled corticosteroids to control their symptoms for at least 1 year. Subjects with sulfite-induced asthma were defined as those experiencing a ≥ 20% decrease in FEV_1 within 30 minutes after one of the oral doses of $K_2S_2O_5$ in capsules, beverages, or lettuce during a double-blind challenge. Sulfite-sensitive subjects with asthma were required to display no response to the placebo segment of the double-blind challenge.

Table I. Characteristics of sulfite-sensitive subjects with asthma

			Single-blind challenge		Double-blind challenge	
Subject	Age and sex	Steroid use	% FEV_1 decrease	Provoking dose*	FEV_1 decrease	Provoking dose*
1	25F	+	> 36	10 (5.8)	27	25 (14.4)
2	33F	+	29	25 (14.4)	NT†	NT†
3	31F	+	62	25‡ (16.8)	36	10 (5.8)
4	41M	+	30	50‡ (33.7)	0	—
5	46F	+	20	10 (5.8)	21	100 (57.6)
6	26M	–	38	200 (115)	28	50 (28.8)
7	25F	+	36	1‡ (0.6)	27	10‡ (5.8)
8	55M	–	20	25 (14.4)	32	5 (2.9)

*Provoking dose in milligrams of potassium or sodium metabisulfite (milligram SO_2 equivalents as determined by calculation and confirmed by analysis of capsules by the modified Monier-Williams method).
†This patient refused to take the double-blind capsule/beverage challenge but was administered a double-blind lettuce challenge; see Table II.
‡Patients 3 and 4 received their initial challenges in apple juice in a single-blind fashion. On subsequent double-blind challenges, they received a capsule/beverage challenge. Patients 4 and 7 responded only to sulfite in beverages and not to sulfite in capsules.

Foods

Dried apricots (Del Monte and Kohl's brand), white grape juice (Meier's catawba grape juice), and dehydrated potatoes (Betty Crocker potato buds) were purchased from a local supermarket. Open containers of these products were not stored for later use because this practice decreases the level of residual sulfite. Dried apricots and white grape juice were used as purchased with no additional preparation. For the one double-blind challenge with white grape juice, the placebo grape juice that had not been sulfited was generously provided by Welch Foods, Inc., and was stored frozen until it was needed. The dehydrated potatoes were rehydrated in boiling water, and margarine, according to the instructions of the manufacturer. Nonsulfited potatoes were prepared by purchasing fresh potatoes, peeling, cooking, and mashing with milk and margarine. Mashed potatoes with intermediate

levels of sulfite were prepared by mixing the potatoes made from sulfited dehydrated potatoes and nonsulfited mashed potatoes. Challenges were begun within l hour of preparation or opening of the packages for these products.

Fresh lettuce was obtained from the supermarket, washed, shredded by hand, and dipped in a sulfite solution. A commercial salad freshener of the type once commonly used by restaurants (Diamond Crystal Fruit & Salad Crisper, Diamond Crystal Salt Company, Wilmington, Massachusetts) that contained sodium bisulfite, citric acid, sodium carbonate, and ascorbic acid was used according to directions of the manufacturer (one tablespoon or 20 gm of salad freshener per gallon of water for the dipping solution and a 30-second dipping time).[11] For one lettuce challenge of a patient with a high threshold for sulfite on capsule/beverage challenge (patient 6, Table II), the dipping solution was made with 60 gm of salad freshener per gallon of water to obtain a more highly sulfited product. The sulfited lettuce was drained, and challenges were begun within 18 hours of preparation, since sulfite residues in lettuce are stable for that period.[11] Nonsulfited lettuce was prepared by washing, shredding, and draining. Challenges with the nonsulfited lettuce were also initiated within 24 hours of preparation.

Table II. Responses of sulfite-sensitive subjects with asthma to challenges with sulfited foods

	Fresh lettuce*			Fresh mushrooms*			Dried apricots		
Subject	Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (gm)	Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (gm)	Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (gm)
1	+[26]	14.6	24	—	24.4	160	+[25]	13.1	4.0
				—	37.8	160			
2	+[29]	71.2	150	—	15.9	160	+[20]	24.5	10.0
				—	28.4	160			
3	+[32]	17.1	33.6	+[28]	4.2	160	NT	NT	NT
4	+[48]	77.3	150	—	8.7	160	—	212	75.0
5	—	57.6	150	NT	NT	NT	—	230	86.5
6	—	57.6	150	NT	NT	NT	—	230	94.0
	—†	225	150						
7	—	46.5	93	NT	NT	NT	—	184	69.3
8	—	75.0	150	NT	NT	NT	—	128	75.0

*These challenges were conducted in a double-blind fashion, whereas all other challenges were open challenges. In all cases except those noted, no reactions occurred during placebo food challenges.

†These challenges were conducted with foods treated with abusive levels of sulfite.

Equiv = equivalent; NT = not tested

White grape juice			Dehydrated potatoes			Shrimp		
Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (ml)	Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (gm)	Response [% ↓FEV_1]	Total SO_2 equiv (mg)	Food (gm)
+[27]	22.1	100	—	16.1	200	—	15.2	150
+[25]	65.0	250	+[20]	15.0	190	—	26.3	150
			—*	21.6	300			
			+*[23]	0	300			
NT	—	—	+[20]	5.8	75	—	11.6	200
—*	61.5	250	—	29.0	300	—	11.8	200
—	111	500	—	17.0	500	—†	115	150
—	115	585	+[25]	28.8	465	—†	115	146
			—*	28.8	384			
—	46.1	259	—*	22.2	300	—†	92.2	117
—	62.8	250	—*	21.3	300	—*	33.0	200

Frozen shrimp were obtained from the supermarket; the heads and shells had been removed, but there had been no further processing. The shrimp were dipped in either a 1.25% or a 5% solution of sodium bisulfite for 5 minutes. The recommended commercial practice is a 1-minute dip in a 1.25% solution of sodium bisulfite.[12] The sulfited shrimp were cooked by boiling in water, and challenges were begun within 1 hour. For the one double-blind challenge, the placebo shrimp were identical frozen shrimp that received no sulfite treatment.

Fresh mushrooms were obtained from a local grower or health food store (growers and distributors attested to no washing procedures for these mushrooms) and washed in a solution of 3000 ppm of sodium bisulfite for 3 minutes with gentle agitation. The mushrooms were drained, covered, and held at 4°C for 24 hours. The recommended industry practice had been a 3-minute dip in a solution of l000 ppm of sodium bisulfite[13]; this practice was banned by the recent FDA prohibition of the use of sulfites on fresh fruits and vegetables.[2] Immediately before challenge, the mushrooms were treated with a nonsulfited lemon juice–olive oil dressing. Nonsulfited mushrooms were prepared by washing with water, draining, holding at 4°C for 24 hours and treating with the lemon juice–olive oil dressing.

Selection of sulfited foods

The foods chosen for these challenges represent a cross-section of the many sulfited foods available in the marketplace. Lettuce was chosen because it can contain high levels of sulfite (500 to 900 ppm total SO_2). Much of the sulfite is present in the free or unbound state, and many of the reported reactions implicate salad bars and lettuce.[11] Fresh mushrooms were chosen because they are a very different type of fresh produce from lettuce in that they contain very low residues of sulfite, < 10 ppm of total SO_2, when mushrooms are treated according to recommended procedures.[13] Dried apricots were selected because they have the highest residual sulfite level of any food in the marketplace[1] and because the sulfite is likely bound to carbohydrate. White grape juice was included because it is an acidic beverage and may most closely mimic the acidic solutions used in capsule/beverage

challenges.[6,14] White grape juice was chosen over wine because many subjects with asthma report a history of adverse reactions to wine, and these reactions may not be attributable solely to the sulfite content of the wine.[8] Some sulfite-sensitive subjects with asthma may react only to sulfite in acidic beverages, such as white grape juice.[14] Dehydrated potatoes were included because they are one of the most commonly consumed of the sulfited foods, and the sulfite is probably bound to starch. Shrimp were selected because they are a common form of sulfited food, and the sulfite is likely bound largely to protein.

Sulfite analysis

The level of residual sulfite in all foods provided for challenge was determined by the titrimetric variation of the modified Monier-Williams method.[15] This procedure measures total sulfurous acid (free sulfite plus some of the bound forms of sulfite) expressed as SO_2 equivalents. The sulfite analyses were performed simultaneously or just before the challenges to ascertain the amount of sulfite in the foods at the time of challenge.

Challenge protocol

On challenge days, patients were permitted to take their usual medications with several exceptions: inhaled β-agonists and sodium cromolyn were withheld for 8 hours and antihistamines were withheld for 12 hours. Baseline pulmonary function tests were performed with a Puritan-Bennett model PS600 spirometer (Madison, Wisconsin) or a MedScience model 25-70 wedge spirometer (Denver, Colorado). The patients were required to have a baseline FEV_1 of no < 70% of their predicted normal and at least 1.5 L. If the patients met these criteria, they were allowed to participate in the food challenges. On subsequent challenge days, the patient's FEV_1 had to be within 10% of the original baseline to qualify for challenges on that particular day. The study had the approval of the University of Wisconsin and Presbyterian/St. Luke's Human Subjects Committee (Institutional Review Board), and all patients signed written informed consent forms before challenges.

Lettuce challenge

The first challenge test was a double-blind lettuce challenge, which was conducted on 3 separate days. Patients were randomly assigned to receive placebo (nonsulfited) lettuce on 2 of the challenge days, and sulfited lettuce on 1 separate day of the challenge trial. Increasing amounts of lettuce were provided at 30-minute intervals, starting with an amount that would contain less than the patient's known provoking dose of sulfites (determined from double-blind capsule/beverage challenges) and ending with either a positive response or 93 to 238 gm of lettuce containing 46.5 to 225 mg of total SO_2 equivalents. FEY_1 measurements were made no later than 30 minutes after each dose of lettuce. A drop in FEV_1 of 20% or more with or without other symptoms, such as cough, was considered a positive response, and the challenge trial for that particular day was terminated.

Fresh mushroom challenge

Fresh mushroom challenges were also conducted in a double-blind manner during a period of 2 or 3 days. Patients were randomly assigned to receive either placebo or sulfited mushrooms on the trial days. Sulfited mushrooms were administered on 1 or 2 of the challenge

days, and placebo mushrooms were administered once. Increasing amounts of mushrooms (60, 110, and 160 gm) were provided at 30-minute intervals. The 160-gm dose of fresh mushrooms contained between 15.9 and 37.8 gm of total SO_2 equivalents. FEV_1 measurements were made as noted above, and the trial was terminated if a positive response occurred.

Dehydrated potato challenge

In six of the eight patients, dehydrated potato challenges were conducted in an open challenge with confirmation of any positive responses with a later double-blind challenge. With the remaining patients, the initial challenge was done double-blind. In one case (patient 3), additional double-blind challenges were performed with potatoes containing varying amounts of residual sulfite. Increasing amounts of potatoes were administered at 30-minute intervals until either a positive response occurred or a maximum dose of 200 to 500 gm of mashed potatoes was consumed containing 16.l to 29.0 mg of total SO_2 equivalents.

Shrimp, dried apricot, and white grape juice challenges

Open challenges were conducted with shrimp (except in one case in which a double-blind challenge was performed), dried apricots, and white grape juice (except in one case in which a double-blind challenge was performed). In the case of shrimp, increasing amounts of shrimp were administered at 30-minute intervals until 117 to 200 gm of shrimp was consumed containing 11.6 to 115 mg of total SO_2 equivalents. With dried apricots, increasing amounts were administered at 30-minute intervals until either a positive response occurred or a maximum dose of 69.3 to 94.0 gm of dried apricots containing 128 to 230 mg of total SO_2 equivalents was consumed. For white grape juice, increasing amounts were administered at 30-minute intervals until either a positive response occurred or a maximum dose of 250 to 585 mg containing 46.1 to 115 mg of total SO_2 equivalents was consumed. Where double-blind challenges were conducted with shrimp and white grape juice, the order of presentation of the sulfited and placebo products was random.

Results

Patient characteristics

Some of the differences within this group of sulfite-sensitive subjects with asthma are presented in Table I. Two of the patients (Nos. 4 and 7) responded only to sulfite solutions and not to sulfite capsules. Among the capsule reactors, threshold levels ranged from 5 to 200 mg of $K_2S_2O_5$, although the threshold levels were not always consistent from the single-blind to the double-blind challenge. In some cases, the variation in threshold levels from one challenge to another were rather substantial; for example, patient 8 had a threshold of 5 mg of $K_2S_2O_5$ on the double-blind trial but had a threshold of 25 mg of $K_2S_2O_5$ on the single-blind trial. Among the solution reactors, threshold levels ranged from 0.6 to 33.7 mg of SO_2 equivalents. Another patient (No. 4) had a negative response to the double-blind capsule/beverage challenge but had positive responses to the single-blind challenge and the double-blind lettuce challenge (Table II). Consequently, he is classified as a sulfite-sensitive subject with asthma.

Food challenges

The results of the challenges of these eight subjects with asthma with various sulfited foods are provided in Table II. Four of the patients (Nos. 5 through 8) failed to react to any of the food challenges. Patient 6 did react to dehydrated potatoes on open challenge, but his reaction to potatoes could not be confirmed by later double-blind challenge.

Four of the patients reacted to one or more of the sulfited foods (Table II). All four subjects reacted to sulfited lettuce in a double-blind challenge that included two placebo challenges with nonsulfited lettuce. Two of three of these patients reacted to challenges with dried apricots and white grape juice; the fourth patient was not challenged with these foods. Only one of the four subjects (No. 3) reacted to challenges with fresh mushrooms or dehydrated potatoes. Another patient (No. 2) reacted to potatoes on open challenge, but on double-blind challenge, the patient responded to the placebo potatoes and not to the sulfited potatoes. Thus, this response has been categorized as a negative reaction to potatoes. Shrimp did not elicit reactions in any of these patients.

Since patient 3 was the only subject to react to challenge with dehydrated potatoes, this response was evaluated in greater detail. As presented in Table III, this patient responded to single-blind and double-blind challenges with dehydrated potatoes having 5. 8 and 9.6 mg of total SO_2 equivalents, respectively. When the patient was evaluated several months later in double-blind challenges with potatoes containing several different levels of residual sulfite, she failed to react to any of the challenges. The levels of sulfite in these challenges at the maximal doses were 0, 3.0, 12.6, and 20.1 mg of total SO_2, respectively.

Patient 3 was also the only patient to react to challenge with sulfited mushrooms. However, she has not been available for more detailed investigation of this response.

Table III. Variability in response to challenges with dehydrated potatoes in a sulfite-sensitive subject with asthma*

	Response	%FEV_1 decrease	Provoking or maximal dose of potatoes (gm)	Provoking or maximal dose of total SO_2 equivalents (mg)
Single-blind challenge	+	20	75	5.8
Double-blind challenges	+	34	125	9.6
		5	300	0
		5	300	20.1
		9	300	12.6
		2	300	3.0
		13	300	0

*Patient 3 from Table II

Sulfite levels in foods

The sulfite levels (in milligrams per kilograms or parts per million of total SO_2 equivalents) found in the sulfited challenge foods, as measured by the Monier-Williams method, were dried apricots (1710 to 3280), fresh lettuce (475 to 515), white grape juice (178 to 260),

mashed potatoes made from dehydrated potatoes (34 to 80), shrimp (58 to 175), and fresh mushrooms (23 to 232).

Discussion

Dosing with sulfited foods

These sulfited food challenges were conducted in a manner intended to simulate the worst situations that could occur with these foods. If reactions did not occur to lower amounts of the foods, the patients were asked to consume a rather large amount of the food, an amount that exceeded any normal serving for that food (Table II). In some cases, the patients were not able to eat the entire upper dose of certain foods (Table II). In most cases, the foods contained typical levels of residual sulfite. Adding additional amounts of sulfite might have altered the fate of sulfite in the food system. For example, it might lead to greater amounts of free sulfite in the food that is definitely a hazardous form of food-borne sulfite.

Several exceptions were made regarding the use of typical levels of sulfite. The potential for excessive use of sulfite is great with lettuce, mushrooms, and shrimp because the sulfite is added, in some cases, by poorly trained and monitored individuals. Such occurrences are unlikely with dehydrated potatoes, dried apricots, and white grape juice in which the sulfite application is done by large food companies with good quality assurance programs that would monitor the levels of sulfite. With mushrooms and shrimp, excessive treatment with sulfites was conducted. The degree of excessive treatment of shrimp with sulfites was modified in the course of these challenges after the FDA issued a regulation that controlled sulfite use in shrimp to a level that would result in residues of ≤ 100 ppm total SO_2. After that point, the target level was 100 ppm total SO_2 in the cooked shrimp; this still represents slight abuse of sulfite because the FDA regulation applies to raw shrimp. With lettuce, excessive treatment with sulfite was used on one occasion with a patient (No. 6) who had a high threshold for sulfite. It was done in an attempt to have sufficient levels of sulfite in the lettuce to induce a reaction, but it was unsuccessful (Table II).

Patient response patterns

Four of the subjects included in this study did not react to any of the sulfited foods, including four of the six patients originally identified as sulfite-sensitive by double-blind capsule/beverage challenges. Patient 6 did react to sulfited potatoes on his initial challenge. However, the lack of confirmation of the initial potato challenge in a subsequent double-blind challenge and the failure to react to other sulfited foods, including some foods with much higher sulfite levels, such as dried apricots, lead to the conclusion that the response to potatoes on open challenge was spurious. Perhaps these patients are not truly sulfite sensitive, although they had positive reactions in a double-blind capsule/beverage challenge.

The remaining four subjects are definitely sulfite sensitive on the basis of reactions to sulfite in capsule/beverage challenges and one or more sulfited foods. Even when subjects are assessed by double-blind capsule/beverage challenges, sulfite sensitivity is a rather rare phenomenon among subjects with asthma occurring in perhaps 3.9% of all subjects with asthma and 8.4% of steroid-dependent subjects with asthma.[7] Even fewer subjects with

asthma appear to respond to sulfited foods based on the negative challenges of four of the six subjects originally identified on the basis of double-blind capsule/beverage challenges.

Patients 1, 2, and 3 had the greatest sensitivities to sulfited foods. All 3 of these patients responded to $K_2S_2O_5$ in capsules at 10 to 25 mg. The same can be said for only one of the patients that failed to respond to any of the sulfited foods (patient 8; Table II). Patient 3 responded to the widest variety of sulfited foods (Table II), although her reactions to dehydrated potatoes were not constant (Table III). Patient 3 also displayed a positive skin test to sulfites by both the prick and intradermal routes[16] that may also indicate a greater degree of sulfite sensitivity. She also had a positive intradermal skin test to acetaldehyde hydroxysulfonate (acetaldehyde bisulfite),[16] which is a major form of bound sulfite in fermented foods, such as wine. This finding may indicate that this patient has a likelihood to react to the bound forms of sulfite that predominate in many foods. Patients l and 2 were also subjected to skin tests with sulfites. Patient 1 had a negative response to an intradermal skin test, whereas patient 2 had a positive intradermal skin test and a negative skin prick test to sulfites. Obviously, several mechanisms may exist for sulfite-induced reactions, even among individuals with reactions to sulfite in capsules. The positive skin tests may indicate the existence of an immunologic response to sulfites, although more proof is needed.

Patient 4 may represent a distinct category of sulfite-sensitive individuals, since he responds to acidic solutions of sulfite and not to capsules (Table I). The mechanism of solution reactions apparently involves inhalation of SO_2 gas evolved from the acidic beverage during ingestion.[14] Patient 4 reacted only to sulfited lettuce among the variety of sulfited foods included in these challenges (Table II).

The variability of positive reactions to sulfited foods encountered in the course of these challenge trials is also noteworthy. As noted in Table III, patient 3 did not react to dehydrated potatoes on some occasions but did on other occasions. Similarly, two other patients (Nos. 2 and 6) reacted to dehydrated potatoes on open challenge but failed to respond appropriately on double-blind challenge. The reasons for such variability are not known at this time, but variability has previously been noted in capsule/beverage challenges.[17] The accuracy of the diagnosis of patient 3 as a sulfite-sensitive subject with asthma might be questioned on the basis of the inconsistent results of challenges with dehydrated potatoes. However, no false positive responses were noted with patient 3 on several blinded capsule/beverage challenges or with a double-blind lettuce challenge that included two placebo challenges. It should be noted that the single-blind and the first of the double-blind challenges of patient 3 with dehydrated potatoes were conducted several months before the final four challenges (Table III). During this period of time, the patient's asthmatic condition had improved considerably.

Correlation of response with sulfite residues

The likelihood of a reaction to a particular sulfited food does not correlate with the amount of sulfite, as measured in total SO_2 equivalents, ingested in the challenge dose. For example, patient l responded to 14.6 mg, 13.1 mg, and 22.1 mg of total SO_2 equivalents in fresh lettuce, dried apricots, and white grape juice, respectively, but failed to react to 24.4 mg, 37.8 mg, 16.1 mg, and 15.2 mg of total SO_2 equivalents in two challenges with fresh mushrooms, dehydrated potatoes, and shrimp, respectively (Table II). Patient 3 failed to react to

shrimp, even though the amount of sulfite present in the maximum dose of shrimp, 11.6 mg, was higher than the amount that provoked reactions to fresh mushrooms and dehydrated potatoes. Patient 4 reacted only to lettuce among the sulfited foods, even though the maximal dose of dried apricots contained 212 mg of total SO_2 equivalents compared to 77.3 mg in the sulfited lettuce (Table II).

In some cases with highly sulfited food, such as lettuce and dried apricots, reactions could be induced by ingestion of only a small amount of the food. For example, reactions occurred to 4 and 10 gm of dried apricots and to 24 and 33.6 gm of lettuce. These amounts of these foods are small by comparison to normal serving sizes.

The form of sulfite present in the food is also likely to affect the likelihood of an asthmatic reaction to ingestion of that particular food. The level of free, unbound sulfite in the food may be particularly important. The capsule/beverage challenges contain entirely free, unbound sulfite. Thus, the very definition of sulfite sensitivity conveys a high likelihood for responsiveness to free sulfite residues in foods. Most sulfited foods contain very little free sulfite; most sulfite added to these foods reacts with various components of the food.[1] Lettuce is an exception and contains a high proportion of free sulfite along with rather high residual levels of sulfite.[11] Also, the salad freshener contains citric and ascorbic acids so that the lettuce may mimic an acidic beverage challenge to some extent. Thus, it is not surprising that lettuce elicited the greatest number of positive reactions (Table II) Howland and Simon[18] previously noted that sulfited lettuce would elicit asthmatic reactions in capsule reactors. Lettuce was the only food to elicit a response in patient 4 who is a solution reactor. This likely reflects the facts that the salad freshener is acidic and that high levels of sulfite were present.

The nature of the bound forms of sulfite that predominate in most foods[1] could have an effect on the likelihood of reactions to sulfited foods. None of the patients reacted to sulfited shrimp, and only one subject reacted to sulfited mushrooms or dehydrated potatoes. In these foods, most of the sulfite is likely bound to protein or starch. However, several patients reacted to dried apricots and white grape juice; most sulfite in these foods is likely bound to sugars. Glucose hydroxysulfonate is a rather unstable bound form of sulfite,[19] which may explain the greater likelihood for reactions to these foods. Of course, dried apricots and white grape juice contain higher residual levels of sulfite than shrimp, potatoes, or mushrooms; therefore, that also is likely to play a role. The fact that the reactions to sulfited foods could not be correlated with the dose of total SO_2 equivalents in the foods (Table II) suggests strongly that the form of sulfite is important. Some patients, such as the capsule reactors, may be more likely to react to bound forms of sulfite than other patients. Patient 3, who has a positive skin test to acetaldehyde hydroxysulfonate,[16] may be especially likely to react to bound forms of sulfite in foods.

Diagnostic considerations

The patient's history is frequently unreliable as an indication of sulfite sensitivity.[8] Preferably, the initial diagnosis of sulfite sensitivity requires a double-blinded capsule/beverage challenge.[5,7] However, four of the eight subjects included in these trials did not react to any of the sulfited foods, suggesting that the positive responses in the double-blind capsule/beverage challenges were false positive reactions. Confirmation of a positive double-blind

capsule-beverage challenge with additional double-blind capsule/beverage challenges or food challenges may be important in making the correct diagnosis. Double-blind lettuce challenges in particular may be an effective alternative to a second confirmatory capsule/beverage challenge.

However, challenges with sulfited foods must be approached with caution. Some sulfited foods contain considerable sulfite and could induce severe reactions in sensitive individuals. For that reason, challenges with highly sulfited foods, such as lettuce and dried apricots, should be conducted only if a reliable, proven method, such as the Monier-Williams method, is available to measure the amount of residual sulfite. Then, the sulfited food should be administered in incremental doses, starting at doses below the patient's threshold for sulfites determined by the capsule/beverage challenge. Challenges with sulfited foods can be conducted safely with these precautions, although the Monier-Williams method would not be conveniently available to many physicians. Challenges with foods containing low residual sulfite levels can be conducted without such analyses if they are approached cautiously and, especially, if the patient gives a history of ingesting such foods without incident. Although such challenges will neither confirm or refute the original diagnosis, the results will provide information on a patient's individual tolerance to specific sulfited foods.

Conclusions

Challenges with a variety of sulfited foods reveal that some sulfited foods may be safe for consumption by sulfite-sensitive subjects with asthma. The likelihood of asthmatic reactions on ingestion of a sulfited food is influenced by numerous variables, including, but not limited to, the patient's threshold of sensitivity to sulfites, the mechanism of sulfite sensitivity for that patient, the level of residual sulfite in the food, the form of sulfite in the food, and amount of food ingested. Variable reactions to certain sulfited foods were also noted in some patients; the reasons for this variability are unknown. These complex interactions make predictions of a patient's likelihood for reaction to a particular sulfited food very difficult without conducting challenges with that food. Challenges with sulfited foods can be conducted safely, if they are approached cautiously, and will provide confirmation of the diagnosis of sulfite sensitivity and information on the patient's sensitivity to particular sulfited foods. Clearly, avoidance diets for sulfite-sensitive subjects with asthma can contain some sulfited foods, especially foods with low residual sulfite levels. Some patients need to be much more cautious than other patients in their consumption of sulfited foods. Skin tests with free and bound forms of sulfite may be of some assistance in identification of the most sensitive patients.

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References

1. Taylor SL, Higley NA, Bush RK. Sulfites in foods—uses, analytical methods, residues, fate, exposure assessment, metabolism, toxicity, and hypersensitivity. Adv Food Res 1986;30:1.
2. Anonymous. Food labelling; declaration of sulfiting agents. Fed Reg 1986;51:25012.
3. Anonymous. Sulfiting agents: revocation of GRAS status for use of fruits and vegetables intended to be served or sold raw to consumers. Fed Reg 1986;51:25021.
4. Anonymous. The reexamination of the GRAS status of sulfiting agents. Bethesda, Md.: Life Sciences Research Office, Federation of American Societies for Experimental Biology, 1985:96.
5. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. J Allergy Clin Immunol 1981; 68:26.
6. Baker GJ, Collett P, Allen DH. Bronchospasm induced by metabisulfite-containing foods and drugs. Med J Aust 1981; 2:644.
7. Bush RK, Taylor SL, Holden K, Nordlee JA, Busse WW. Prevalence of sensitivity to sulfiting agents in asthmatic patients. Am J Med 1986;81:816.
8. Bush RK, Taylor SL, Busse W. A critical evaluation of clinical trials in reactions to sulfites [Symposium]. J Allergy Clin Immunol 1986;78:191.
9. Meggs WJ, Atkins FM, Wright R, Fishman M, Kaliner MA, Metcalfe DD. Failure of sulfites to produce clinical responses in patients with systemic mastocytosis or recurrent anaphylaxis: results of a single-blind study. J Allergy Clin Immunol 1985;76:840.
10. Koepke JW, Christopher KL, Chai H, Seiner JC. Dose-dependent bronchospasm from sulfites in isoetharine. JAMA 1984:251:2982.
11. Martin LB, Nordlee JA, Taylor SL, Sulfite residues in restaurant salads. J Food Prot 1986;49:126.
12. Finne G, Wagner T, DeWitt B, Martin R. Effect of treatment, ice storage, and freezing on residual sulfite in shrimp. J Food Sci 1986;51:231.
13. Beelman RB, Barden CL, Edward CG. Total sulfur dioxide residuals in fresh mushrooms washed in sulfite solutions [Abstract]. Dallas: Forty-sixth Annual Institute Food Technologists Meeting. 1986:110.
14. Delohery J, Simmul R, Castle WD, Allen DH. The relationship of inhaled sulfur dioxide reactivity to ingested metabisulfite sensitivity with asthma. Am Rev Respir Dis 1984;130:1027.
15. Williams S, ed. Official methods of analysis of the Association of Official Analytical Chemists. 14th ed. Arlington:·Association of Official Analytical Chemists, 1984:391–2.
16. Selner J, Bush R, Nordlee J, Wiener M, Buck1ey J, Koepke J, Taylor S. Skin reactivity to sulfite and sensitivity to sulfited foods in a sulfite-sensitive asthma [Abstract]. J Allergy Clin Immunol 1987;79:241.
17. Lee RJ, Braman SS, Settipane GA. Reproducibility of rnetabisulfite challenge [Abstract]. J Allergy Clin Immunol 1986;77:157.
18. Howland WC, Simon RA. Restaurant-provoked asthma: ? Sulfite sensitivity [Abstract]. J Allergy Clin Immunol 1985:75:145.
19. Green LF. Sulphur dioxide and food preservation—a review. Food Chem 1976:1:103.