11-1986

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Published in *The American Journal of Medicine* 81 (November 1986), pp. 816–820; doi: 10.1016/0002-9343(86)90351-7

Submitted November 6, 1985; accepted November 27, 1985.

Prevalence of Sensitivity to Sulfiting Agents in Asthmatic Patients

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Abstract

Ingestion of sulfiting agents can induce wheezing in some asthmatic patients. However, neither the prevalence of sulfite sensitivity nor the clinical characteristics of the affected asthmatic population are known. In a prospective single-blind screening study, 120 non-steroid-dependent and 83 steroid-dependent asthmatic patients underwent challenge with oral capsules of potassium metabisulfite. Five non-steroid-dependent and 16 steroid-dependent asthmatic patients experienced a greater than 20 percent reduction in their one-second forced expiratory volume within 30 minutes following the oral challenge. Twelve of these sulfite reactors were rechallenged with metabisulfite capsules in a double-blind protocol. Under these conditions, only three of seven steroid-dependent patients had a positive response. Moreover, only one of five non-steroid-dependent patients had a response to double-blind challenge. On the basis of this challenge study, the best estimate of the prevalence of sulfite sensitivity in the asthmatic patients studied is 3.9 percent. This population, however, contained a larger number of steroid-dependent asthmatic patients than would be found in the general asthmatic population. It is concluded, therefore, that the prevalence of sulfite sensitivity in the asthmatic population as a whole would be less than 3.9 percent and that steroid-dependent asthmatic patients are most at risk.

Sulfiting agents, including sulfur dioxide, sodium and potassium bisulfite, sodium and potassium metabisulfite, and sodium sulfite, have been used for centuries in food processing

and as food preservatives. The term "sulfite sensitivity" is used to describe the adverse reactions experienced by patients upon ingestion of sulfiting agents. Although these agents are apparently judged to be safe for normal persons, recent reports [1–4] indicate that asthmatic patients are highly susceptible to bronchospasm following sulfite injestion. The mechanism(s) responsible for these reactions are not completely understood. In some instances, an immunologic basis [5] may be involved, although the bronchospastic response is believed to be mediated through the stimulation of airway irritant receptors by inhaled sulfur dioxide [6]. In addition, some asthmatic patients may not be able to metabolize sulfiting agents properly because of a deficiency of the enzyme sulfite oxidase [7].

Because of the convincing evidence that links episodes of bronchospasm to sulfite ingestion, attempts have been made to determine the prevalence of sulfite sensitivity in asthmatic subjects (Table I). Since the patients incorporated in these series most likely had more severe asthma than the asthmatic population as a whole, the prevalence of sulfite sensitivity in asthmatic patients may be overestimated. However, because sulfiting agents can pose a severe risk for selected asthmatic patients, it is essential that these estimates of the frequency of sulfite sensitivity be confirmed and that the characteristics of the population-at-risk be defined. To accurately diagnose sulfite sensitivity, a carefully conducted provocative challenge is necessary. The following reports our experience with oral metabisulfite challenges conducted in 203 asthmatic patients.

Table I. Preliminary Reports of Prevalence of Sulfiting Sensitivity in Asthmatic Patients

Reference	Number of Patients	Prevalence (percent)	Comments
Simon RA, Green L, Stevenson DD: J Allergy Clin Immunol 1982; 69: 118	61	8.2	Patients without clinical history of sulfite sensitivity. Large portion of steroid-dependent asthmatic patients. Confirmatory placebo-controlled challenges performed.
Koepke JW, Selner JC: Ann Allergy 1982; 48: 258	15	7.0	Patients with history of possible sulfite reactions. Largely steroid-dependent. Single-blind challenges only.
Buckley CE III, Saltzman HA, Sieker HO: J Allergy Clin Immunol 1985; 75: 144	134	4.6	Single-blind challenges only. Probably large portion of steroid dependent asthmatic patients.

Patients and Methods

Patient Population

Two hundred three adult patients attending the University of Wisconsin Allergy Clinic participated in the study. Patients were selected for the study on the basis of the presence

of asthma; they were not selected for a history of adverse reaction to sulfites. This large population of patients were divided into steroid-dependent and non-steroid-dependent groups. The steroid-dependent patients were defined as those requiring either oral (daily or alternate-day) or daily inhaled corticosteroids to control their symptoms for at least one year. Corticosteroid use in these patients was justified on the basis of persistent airway obstruction (despite intensive treatment with oral and inhaled bronchodilators), which responded to steroid therapy. Therefore, we assumed that the steroid-dependent patients had more severe asthma. The study had the approval of the University of Wisconsin Human Subjects Committee, and all patients signed written informed consent forms prior to the challenge.

Sulfite Challenge Procedure

The sulfite challenge procedure was divided into two phases. In the first phase, we used a single-blind challenge as a screening test, since this required only one day of the patient's time. In the second phase, patients who showed response to the single-blind challenge were asked to return for a confirmatory double-blind challenge.

Single-Blind Challenge

On the day of challenge, patients reported to the pulmonary function laboratory. They were permitted to take their usual medications, with the following exceptions: both inhaled beta-agonists and sodium cromolyn were withheld for eight hours, and antihistamines were withheld for 12 hours.

Baseline pulmonary function tests were performed using a Puritan-Bennett (model PS 600) or a Vitalograph (model 490000) spirometer. On the study day, patients were required to have a baseline one-second forced expiratory volume of no less than 70 percent of predicted normal and at least 1.5 liters. After meeting these requirements, the patients were given oral metabisulfite challenges.

For the challenge, size 00 gelatin capsules (E. Lilly and Company, Indianapolis, Indiana) were filled with either reagent grade potassium metabisulfite (J. T. Baker Company, Phillipsburg, New Jersey) mixed with sucrose (Sigma Chemical Company, St. Louis, Missouri) or sucrose alone. The sucrose had been powdered in a food mill. The initial capsule given in all challenges contained the sucrose placebo. If there was no change in the one-second forced expiratory volume 30 minutes later, the patient was given capsules containing one, five, 10, 25, 50, 100, and 200 mg of the potassium metabisulfite at successive 30-minute intervals. Pulmonary functions were determined at the end of each of the 30-minute intervals. The challenge was considered positive and no further capsules were given if the one-second forced expiratory volume dropped at least 20 percent from baseline. If no change in pulmonary function was noted during capsule dosing, the patients were challenged at 30-minute intervals with 1, 10, and 25 mg doses of potassium metabisulfite mixed with sucrose in distilled water. Pulmonary functions were again measured every 30 minutes after dosing. Again, a positive response to metabisulfite was interpreted as a 20 percent or greater fall in one-second forced expiratory volume. Patients who experienced an asthmatic episode as a result of the challenge were treated with sulfite-free aerosol bronchodilators, injectable epinephine, and other supportive measures as needed. Resuscitative

equipment, including measures for endotracheal intubation and mechanical ventilation, was immediately at hand. Patients who did not show a response to the single-blind challenge with a 20 percent or greater drop in one-second forced expiratory volume were considered not to be sulfite-sensitive. We have conducted repeated single-blind challenge in five persons (three non-steroid-dependent and two steroid-dependent), none of whom reacted.

Double-Blind Challenges

Patients who showed a positive response to the single-blind challenge were asked to return for a double-blind challenge. This was conducted on two separate days. Patients were randomly assigned either to receive sucrose-containing placebo capsules or to be rechallenged with increasing doses of potassium metabisulfite in identical fashion to the single-blind protocol. On a separate occasion at least three days after the initial challenge, the subjects received the material not administered on the first day.

Results

The results of the single-blind and double-blind challenges and estimates of the prevalence of sulfite sensitivity are summarized in Tables II and III. Of 83 steroid-dependent asthmatic patients challenged, 16 had a positive reaction. This gives a prevalence of sulfite sensitivity of 19.6 percent in our population. In contrast, only five of the 120 non-steroid-dependent asthmatic patients had a drop in one-second forced expiratory volume when challenged with sulfite-containing capsules (4.2 percent prevalence).

Table II. Asthmatic Patients with Response to Sulfite Challenge

			Single-Blind Challenge				Double-Blind Challenge*						
							Placebo			Potassium Metabisulfite			
Subject	Age and Sex	Steroid Use	Percent FEV_1 Decrease	Provoking Dose (mg)	Wheezing	Treatment†	Percent FEV_1 Decrease	Wheezing	Treatment†	Percent FEV_1 Decrease	Wheezing	Treatment†	Interpretation
1	19F	+	21	100	—	A	NT	NT	NT	NT	NT	NT	
2	24F	+	29	50	+	A	21	—	A	19	—	—	Negative
3	23F	—	25	5	—	A, B, C	28	—	A	3	—	—	Negative
4	38M	+	> 30	100	+	A	NT	NT	NT	NT	NT	NT	
5	46F	+	20	10	—	A, B	10	—	—	21	—	A	Positive at 100 mg
6	25F	+	> 36	10	+	A	2	—	—	27	+	A, C	Positive at 25 mg
7	40M	+	33	10	+	A	NT	NT	NT	NT	NT	NT	
8	47F	+	29	5	—	A	NT	NT	NT	NT	NT	NT	
9	40M	+	30	10	—	A	13	—	—	8	—	—	Negative
10	19M	—	20	25	—	A	19	—	A	0	—	—	Negative
11	26F	+	28	50	+	A	NT	NT	NT	NT	NT	NT	
12	41M	+	20	100	—	A	16	—	—	0	—	—	Negative
13	22F	+	20	25 (solution)	—	A	NT	NT	NT	NT	NT	NT	
14	36M	+	28	50	—	A, B	NT	NT	NT	NT	NT	NT	
15	32F	+	34	200	—	A, B, C	NT	NT	NT	NT	NT	NT	
16	26M	—	38	200	+	A	0	—	—	28	+	A, C	Positive at 50 mg
17	19F	—	21	50	+	A	0	—	—	6	—	—	Negative
18	26F	+	20	1 (solution)	—	A	20	—	A	20	+	A	Negative
19	21F	—	28	5	+	A	35	+	A, B, C	0	—	—	Negative
20	33F	+	29	25	—	A	NT	NT	NT	NT	NT	NT	
21	25F	+	36	1 (solution)	+	A, B, C	17	—	—	27	+	A	Positive at 10 mg

*Placebo and potassium metabisulfite challenges conducted in random sequence.

†A = two inhalations from a metered-dose aerosol bronchodilator, B = subcutaneous epinephrine, C = nebulized terbutaline

FEV_1 = one-second forced expiratory volume; NT = not tested

Table III. Prevalence of Sulfite Sensitivity

Single-Blind Challenges (n = 203)	
Steroid-dependent (n = 83)	Non-steroid-dependent (n = 120)
Number of Patients with Responses (n = 21)	
Steroid-dependent patients with response (n = 16)	Non-steroid-dependent patients with response (n = 5)
Estimated prevalence in our steroid-dependent patients based on single-blind challenges (16/83) = 19.3%	Estimated prevalence in our non-steroid-dependent patients based on single-blind challenges (5/120) = 4.2%
Estimated overall prevalence of sulfite sensitivity in our population based on single-blind challenges = (21/203) = 10.3%	
Double-Blind Challenges (n = 12)	
Steroid-dependent (n = 7/16 single-blind challenges with response)	Non-steroid-dependent (n = 5/5 single-blind challenges with response)
Number of Patients with Responses (n = 4)	
Steroid-dependent patients with response (n = 3; 3/7 = 42.9%)	Non-steroid-dependent patients with response (n = 1; 1/5 = 20%)
Estimated prevalence in our steroid-dependent patients based on double-blind challenges (3/83 = 3.6%* – [7/83 = *8.4%*]† – 12/83 = 14.5%‡)	Estimated prevelance in our non-steroid-dependent patients based on double-blind challenges (1/20 = *0.8%*)
Estimated overall prevalence of sulfite sensitivity in our population based on double-blind challenges (4/203 = 1.9%* – [8/203 = *3.9%*]† – 13/203 = 6.4%‡)	

Estimated prevalence range makes the following assumptions:
*Assumes 0 percent of steroid-dependent subjects not challenged had a positive response to double-blind challenge.
†Assumes 42.9 percent of steroid-dependent subjects not challenged would have a positive response to double-blind challenge.
‡Assumes 100 percent of steroid-dependent subjects not challenged would have a positive response to double-blind challenge.

On the basis of later studies in which we conducted double-blind sulfite challenges, these estimates for the frequency of sulfite sensitivity are inflated. By double-blind challenges, only three of seven (42.9 percent) steroid-dependent asthmatic patients reacted. Moreover, only one of the five non-steroid-dependent asthmatic patients had a drop in one-second forced expiratory volume of 20 percent. Thus, by double-blind challenge, a considerable number of patients with a response to the single-blind challenge did not react. Unfortunately, only seven of 16 steroid-dependent patients agreed to participate in the double-blind challenges.

On single-blind challenge, nine of 16 subjects had wheezing by auscultation together with a 20 percent or greater drop in one-second forced expiratory volume. Five persons received subcutaneous epinephrine in addition to their metered-dose aerosol bronchodilator, whereas three subjects required further treatment with nebulized terbutaline solution to relieve their asthma symptoms (Table II).

On double-blind testing, three of the four sulfite-sensitive asthmatic patients had wheezing (Table II); one patient (Subject 18) experienced wheezing with sulfite but

manifested a 20 percent drop in one-second forced expiratory volume with placebo. This subject did not appear to be sulfite-sensitive in subsequent challenge studies.

In patients undergoing double-blind metabisulfite challenges, we found no correlation between the patient's reported reaction to sulfited food such as wine, dried fruit, or restaurant meals and the response to oral provocation [8]. Subjects 6 and 16 had histories suggestive of sulfite sensitivity whereas Subjects 5 and 21 did not.

Comments

For asthmatic patients with sulfiting agent sensitivity, the ingestion of these preservatives can provoke a severe episode of airway obstruction. But who are the patients at risk and what is the prevalence of sulfite sensitivity in the asthmatic population? Currently, answers to these questions are still conjectural. The earlier estimates by Stevenson and Simon [9] placed the frequency of sulfite sensitivity at 5 to 10 percent of all asthmatic patients, which suggests a major problem for thousands of patients. However, although sulfite sensitivity looms as a major risk for many asthmatic patients, our findings would indicate that the overall prevalence of this problem is less than previously projected and is largely confined to patients with steroid-dependency (i.e., more severe asthma).

Several factors may account for the differences in the results of the observed prevalence of sensitivity to sulfiting agents in our study compared with others. Towns and Mellis [10] found no reactors to a capsule challenge with sulfiting agents in a pediatric population; virtually all of them were steroid-dependent. They did, however, find that 66 percent (19 of 29) of these children reacted to sodium metabisulfite administered in an acidic solution. We administered the sulfiting agent in a capsule form. This method (1) allowed us to blind our experiments appropriately and (2) eliminated the possibility that the subjects were reacting to inhaled sulfur dioxide that may be generated when sulfiting agents are administered in solutions, particularly acidic solutions. Furthermore, when we did administer solutions, they were given in concentrations that allowed us to disguise the taste; and they were maintained at neutral pH in order to avoid the generation of volatile sulfur dioxide that could be inhaled, thus triggering an asthmatic response. Finally, it should be pointed out that capsule and solution challenges may not be comparable to sulfited food challenges.

The importance of single-blinded versus double-blinded challenges in these studies was readily apparent. Only three of seven steroid-dependent and one of five nonsteroid-dependent patients who were considered a positive response on the single-blind challenge had a positive response on subsequent double-blind challenge. Thus, between 55 and 80 percent of the patients challenged using a single-blind protocol would have an erroneous diagnosis of sulfite sensitivity. This fact obviously has important therapeutic implications, particularly with respect to avoidance diets. Likewise, double-blind challenge is of particular concern in the steroid-dependent group. These patients are known to have labile pulmonary function, and the mere withholding of aerosolized bronchodilators for four and a half to five hours during the challenge may have contributed to the observed decreases in one-second forced expiratory volume. Therefore, such observed decreases may be erroneously attributed to sulfite effects. Attempts were made to minimize this possibility by

requiring that the patients have relatively stable pulmonary functions with predicted one-second forced expiratory volume of greater than 70 percent of predicted normal and greater than 1.5 liters.

In a large group of asthmatic patients, our best estimate of the prevalence of sulfite sensitivity in our population is 3.9 percent. This figure is undoubtedly an overestimate, since our patient population contained a larger percentage of steroid-dependent patients than is found in the general asthmatic population. It is essential to stress that we found less than 1 percent (0.8 percent) of nonsteroid-dependent asthmatic patients to be affected. In the steroid-dependent group, our best estimate of sulfite-provoked asthma is 8.4 percent. Therefore, although sulfiting agents pose a risk in asthma, the population in jeopardy appears to be the steroid-dependent group. This does not minimize the risk of sulfite sensitivity but more precisely identifies the patient in jeopardy.

Acknowledgments – This work was supported in part by contributions from the Corn Refiners Association, National Fisheries Institute, National Cherry Growers and Industries Foundation, FritoLay, Inc., R. T. French Co., Basic American Foods, Thomas J. Lipton, Inc., Del Monte Corporation, Hershey Foods Corporation, and Stauffer Chemical Company.

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