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Abstract
Sulfiting agents, including sodium and potassium bisulfite, sodium and potassium metabisulfite, sodium sulfite, and sulfur dioxide, have enjoyed widespread use as food and drug ingredients. The oral ingestion of these sulfiting agents is now known to trigger asthma in a small subset of the asthmatic population. The best evidence suggests that perhaps 150,000 to 200,000 individuals in the United States may be sulfite sensitive. Although the mechanism of sulfite-induced asthma remains unknown, several possibilities have been considered, including inhalation of sulfur dioxide (SO_2) while swallowing, an IgE-mediated reaction, and a deficiency of sulfite oxidase leading to impaired sulfite metabolism and excretion. The only treatment for sulfite sensitivity is avoidance of sulfites in foods and drugs.

Background

Sulfiting agents have been used as food and drug ingredients for many years. The ancient Romans and Egyptians may have been the first to use sulfites as food ingredients by burning sulfur (and creating SO_2) to sanitize wine vessels. Sulfites possess a number of desirable technical attributes as food ingredients, including the control of enzymatic and nonenzymatic browning, antimicrobial effects, dough conditioning, antioxidant actions, and bleaching (1–3). Table 1 contains examples of foods in which sulfites are commonly used for these various technical attributes; it is not intended to be a complete list of all possible sulfited foods. In drugs, sulfites are typically used as antioxidants (4). Recently, the number of foods and drugs containing sulfites has diminished as a result of concern about adverse reactions and restrictions imposed by the Food and Drug Administration (FDA). Alternatives to sulfites, where available and feasible, have been rather widely adopted.

Table 1. Common uses of sulfites in foods

Use	Example
Control of enzymatic browning	Lettuce,* guacamole,* fresh fruit,* fresh mushrooms,* fresh potatoes,* shrimp
Control of nonenzymatic browning	Dehydrated potatoes, dried fruits, white grape juice, white wine
Antimicrobial action	Wines, corn syrup, table grapes
Dough conditioning	Frozen pizza and pie doughs
Bleaching agent	Maraschino cherries, hominy

*Use of sulfiting agents in these products is no longer allowed.

The earliest reports of sulfite sensitivity appeared in the late 1970s (5–7) but were considered isolated case reports and were largely ignored. In 1981, multiple cases of sulfite-induced asthma were reported by Stevenson and Simon (8) and by Allen and Collett (9) at the annual meeting of the American Academy of Allergy and Immunology. These cases were described in journal articles later that same year (10, 11). These reports served to focus attention on sulfites as previously unidentified triggers of asthma. In the ensuing years, many other cases of sulfite sensitivity have been reported in the medical literature; these case reports have been throughly reviewed elsewhere (1, 12–16). Sulfite sensitivity is now a well-accepted medical phenomenon. Most of the described cases involved asthmatic reactions, and the reports of other symptoms have not been widely confirmed and may, in some instances, have resulted from routes of administration other than the oral route (1, 6, 17–21). For that reason, the remainder of this review will focus on sulfite-induced asthma.

Current Status

Although the use of sulfites in foods and drugs has diminished since 1981, sulfiting agents continue to enjoy rather widespread use. Numerous sulfite alternatives have been developed to control enzymatic browning, but effective replacements for sulfites for the control of nonenzymatic browning, for the control of certain undesirable bacteria, and for bleaching purposes are not yet possible.

The level and nature of sulfite residues in foods vary widely (1, 2). Therefore, the tolerance of sulfite-sensitive asthmatics for sulfites must be considered in the development of effective avoidance diets. Also, the form of sulfite in foods may affect the likelihood of reactions to specific sulfited foods.

Chemistry of Sulfites in Foods and Drugs

Sulfur dioxide (SO_2) and the sulfite salts readily dissolve in water and, depending upon the pH of the medium, can exist as sulfurous acid (H_2SO_3), bisulfite ion (HSO_3^-), or sulfite ion (SO_3^{2-}) (12). Most sulfites in foods and all sulfites in drugs are added to achieve some technical benefit, as noted above. However, in foods. and beverages fermented by yeasts, such as wines and beers, sulfites can occur naturally as products of the fermentation process.

The various forms of sulfite are highly reactive, and in foods, sulfites can react with a variety of food constituents, including reducing sugars, proteins, lipids, starch and other

complex carbohydrates, vitamins, and many others (1, 12). The stability of these various forms of bound sulfites is quite variable (1); some of these reactions are readily reversible, whereas others are virtually irreversible. The dissociable forms of bound sulfite can serve as reservoirs for "free" sulfites, while the nondissociable forms serve to remove sulfites permanently from the pool of free sulfites that may exist in sulfited foods. The concept of free sulfites is an important one because sulfite-sensitive asthmatics are most likely to respond to free sulfites (1, 12). Thus, foods with significant levels of residual free sulfites may cause more problems than foods with similar levels of irreversibly bound sulfites. In pharmaceutical preparations, sulfites are more likely to exist in the free, unbound state.

Detection, Residual Levels, and Consumer Exposure

Several methods exist for the detection of sulfite residues in foods (1). The method officially accepted by the Association of Official Analytical Chemists (AOAC) is a distillation-titration procedure known as the Monier-Williams method (22). This method detects "total SO_2," which includes any free sulfites plus any reversibly bound sulfites that can be released under the acidic distillation conditions. However, despite the claim that this method detects total SO_2, irreversibly bound forms of sulfite are not detected (1, 2). No known method is available for detecting all bound forms of SO_2, and available methods vary in their abilities to detect the reversibly bound forms of sulfite. Sulfite-sensitive asthmatics are definitely sensitive to free sulfites, but their degree of sensitivity to the various forms of reversibly and irreversibly bound sulfites remains to be determined. Therefore, the value of the various analytical methods in detecting clinically relevant forms of sulfite in foods and drugs is unknown.

Several types of test strips have been developed for the rapid detection of sulfites by sensitive consumers. Recent evaluations have demonstrated that these test strips are plagued by false-positive and false-negative reactions, which has led to recommendations against their use by consumers (23).

The levels of residual sulfite in foods are highly variable (2). Sulfite levels are highest, exceeding 1,000 parts per million (ppm) total SO_2, in dried fruits, with the exception of dark raisins and prunes, which are not sulfited. Other foods containing in excess of 100 ppm total SO_2 as consumed are wine, nonfrozen lemon and lime juice (frozen citrus juices are not sulfited), sauerkraut juice, and molasses (2, 24). Even in these highly sulfited foods, the level of residual sulfite depends on the exact formulation, the effectiveness and use of sulfite alternatives, and a variety of other factors. Sulfite levels in wines, for example, can vary from 10 to 350 ppm depending on the variety of grapes, sugar content, and other factors. Foods commonly having residual total SO_2 levels between 50 and 100 ppm as consumed include prepared dehydrated potatoes, packaged fresh hash brown potatoes, white and pink grape juices, some sauces and gravies, some fruit toppings, and maraschino cherries (2, 24). Many other foods contain lower residual levels of sulfites (2, 24). The lower limit of detection of the Monier-Williams method is 10 ppm total SO_2.

The FDA and the Bureau of Alcohol, Tobacco, and Firearms (BATF) now require a label declaration of sulfites on foods and wines having residual sulfite levels higher than 10 ppm total SO_2. In addition, sulfite use in fresh fruits and vegetables, with the exception of potatoes, is no longer allowed, and the FDA is actively considering some restriction on sulfite

use in fresh potatoes. These restrictions were imposed because sulfite use in these foods was occasionally substantial (2, 25), and these uses, which were most often practiced by restaurants, could not be effectively labeled.

Overall consumer exposure to ingested sulfites is difficult to determine with any accuracy. The average daily per capita intake of sulfites in foods has been estimated at 6 mg of SO_2 equivalents for nonalcohol users and 10 mg for consumers of wine and beer (24). However, it is quite easy to exceed these average figures at an individual meal. For example, 200 ml of wine containing 150 ppm total SO_2 would contribute 30 mg of SO_2 equivalents, and 50 g of dried apricots containing 2000 ppm total SO_2 would contribute 100 mg of SO_2 equivalents. The amount of sulfite exposure through pharmaceutical preparations is quite variable and dependent upon specific formulations and uses.

Metabolism of Sulfites

Sulfites taken orally are quickly absorbed. In most cases, sulfites are also quickly metabolized via mitochondrial sulfite oxidase, more precisely known as sulfite:O_2 oxidoreductase (EC 1.8.3.1). The product of this reaction is sulfate, which is rapidly excreted in the urine. In humans, sulfite oxidase, which has a substantial metabolic capacity, is the terminal step in the metabolism of both exogenous and endogenous sulfite. Endogenous sulfite arises from the metabolism of the sulfur-containing amino acids, cysteine and methionine. In most cases, an extra exogenous load of ingested sulfite will be excreted quantitatively in the urine as sulfate.

Very little information is known regarding the metabolism of the various bound forms of sulfite that would be predicted to predominate in most sulfited foods. Metabolism of these bound forms of sulfite may depend on the likelihood that they will dissociate (1). Sulfite bound to proteins and administered orally is metabolized to sulfate and excreted in much the same manner as free sulfite (26). A possibly more stable form of bound sulfite, 3-deoxy-4-sulfohexosulose, was largely excreted in the feces after oral administration, suggesting that it was not efficiently absorbed (27).

The subjects of sulfite metabolism and toxicity have been more thoroughly reviewed elsewhere (1, 15, 28, 29).

Sulfite-lnduced Asthma

The prevalence of sulfite sensitivity is a subject of some debate (13). In a controlled, double-blind challenge trial, several hundred nonselected asthmatics were given capsules and neutral solutions containing potassium metabisulfite ($K_2S_2O_5$). The prevalence of sulfite sensitivity was estimated at about 8.4% of the severely affected or steroid-dependent asthmatic population, or about 150,000 individuals in the United States (30); other estimates, based on capsule and acidic beverage challenges, range from 500,000 to 1 million individuals (13). The use of acidic solution challenges would probably have increased the prevalence estimates of Bush et al. (30). Severe asthmatics, defined as those patients who require steroid-based drugs for the control of their symptoms, are at much greater risk of sulfite sensitivity; only rare cases of sulfite sensitivity have been described in nonsteroid-dependent asthmatics (30). The consequences of sulfite-induced asthma can be quite severe, and several deaths have been attributed to sulfite-induced asthma (31, 32).

The diagnosis of sulfite-induced asthma ideally includes a double-blind challenge trial (12, 13). A diagnosis on the basis of dietary history is virtually impossible since sulfites occur in so many different foods in such widely varying amounts. The current ideal design of a double-blind sulfite challenge trial has been described by Simon (13). The challenge trial is conducted with acidic solution doses ranging from 1 to 200 mg of $K_2S_2O_5$. Historically, capsules containing $K_2S_2O_5$ have also been used in these trials, but acidic beverage challenges are now favored because they are more effective in identifying potential sulfite-sensitive asthmatics. The double-blind, placebo-controlled design of the trial is critical because false-positive responses can easily be observed with asthmatic subjects.

Sulfite-sensitive asthmatics display threshold responses to controlled challenges with sulfites. Asthmatic reactions have been reported to the administration of 1 mg of $K_2S_2O_5$ (about 0.6 mg of SO_2 equivalents), but such responses are rare (13). Most sulfite-sensitive asthmatics have thresholds between 20 and 50 mg of $K_2S_2O_5$ (12 and 30 mg of SO_2 equivalents) (13). It is important to note that some sulfited foods would be unlikely to provide sufficient sulfite in a single meal to trigger an asthmatic response.

The relevance of the various clinical challenge procedures to the likelihood of identification of individuals with sensitivities to sulfited foods has been questioned (1). Certainly, these challenges identify individuals who are likely to respond under some circumstances to sulfited foods. In the acidic beverage challenges, SO_2 is released from the solution in the mouth, and the response may be caused by inhalation of that irritant gas while swallowing (33). The acidic beverage challenge would mimic those sulfited foods and beverages that contain free sulfite in acidic solutions. Examples include wines, white and pink grape juice, nonfrozen lemon and lime juice, and possibly sulfited fresh fruits and lettuce. Over the past 7 years, many alleged incidents of sulfite-induced asthma occurred in restaurants from the consumption of salad bar items such as lettuce, fresh fruits, and guacamole. Many of the incidents implicated lettuce, a food known to contain a large amount of free sulfite with little bound sulfite (25). Sulfites are no longer allowed in fresh fruits and vegetables other than potatoes, since the individuals identified by the acidic beverage challenge protocol were likely to be at risk in such situations. However, some question remains regarding their sensitivity to other sulfited foods where the sulfite is not present in an acidic environment and/or where much of the sulfite may be bound to other food constituents. The capsule challenge would identify individuals likely to react to both acidic and nonacidic sulfited foods but does not indicate the likelihood of reactivity toward bound forms of sulfite (1). Thus, the capsule challenge may still have some clinical value.

Few trials have actually evaluated the sensitivity of sulfite-sensitive asthmatics to sulfited foods. Halpern et al. (34) tested 25 nonselected asthmatics with 4 ounces of white wine containing 160 mg SO_2 equivalents per liter. Only 1 of 25 patients exhibited reproducible symptoms, but the patients were not prescreened for sulfite sensitivity by standard protocols. Howland and Simon (35) conclusively demonstrated that sulfited lettuce can trigger reactions in confirmed sulfite-sensitive asthmatics. Taylor et al. (36) assessed the sensitivity of eight sulfite-sensitive asthmatics, as confirmed by double-blind capsule-beverage challenges, to a variety of sulfited foods including lettuce, shrimp, dried apricots, white grape juice, dehydrated potatoes, and mushrooms. Despite the positive double-blind challenges, four of these patients failed to react to any of the sulfited foods or beverages. The

other four patients experienced a decrease in pulmonary function on double-blind challenges with sulfited lettuce, although for one patient this was the only positive food challenge. Two of the three remaining patients reacted to dried apricots and white grape juice; the other patient did not complete these challenges. Only one of these three patients reacted to challenges with dehydrated potatoes and mushrooms, and in the case of the dehydrated potatoes, the response to multiple double-blind challenges was not consistent. None of these patients responded to sulfited shrimp. Although these results were somewhat confusing, they indicate that sulfite-sensitive asthmatics will not always react to the 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 sulfite-induced asthma (36).

The mechanism of sulfite-induced asthma remains a mystery. Delohery et al. (33) rather elegantly demonstrated that some, but not all, consumers will inhale SO_2 as they swallow an acidic sulfited beverage. The mechanism of the response to acidic beverage challenges is probably the inhalation of SO_2 and its action on irritant receptors in the lung (13, 33); these receptors remain poorly defined. Another possible mechanism is IgE-mediated immediate hypersensitivity. In rare instances, positive skin test responses to sulfite that can be passively transferred or demonstrations of the release of histamine from leukocytes in vitro are observed (6, 13, 21, 31, 37). Sulfite could have the potential to react with proteins and act as a hapten inducing an immunologic response. However, this mechanism does not seem to account for most cases of sulfite sensitivity. A third potential mechanism that could contribute to sulfite sensitivity is a deficiency of sulfite oxidase. Evidence indicates that some sulfite-sensitive asthmatics possess intermediate levels of sulfite oxidase activity, perhaps because they are heterozygotes for sulfite oxidase deficiency (13, 15). Further studies will be needed to confirm these preliminary observations.

Future Directions

Although sulfite-induced asthma is now an accepted medical phenomenon, the prevalence is much lower than originally speculated. The realization that sulfites are a minor trigger of asthma will probably lead to diminished clinical attentiveness to this factor. Progress in understanding the mechanism of sulfite-induced asthma has been, and will continue to be, limited by the small number of sulfite-sensitive subjects to use in clinical experiments and the lack of an animal model of the condition. The major unanswered questions involve the mechanism of sulfite-induced asthma and the forms of sulfite that will trigger asthmatic reactions. Answers to these basic questions may lead to research on improving methods for the detection of sulfites in foods and on effective therapeutic measures. Because of the severe limitations mentioned above, progress is likely to be slow. In the meantime, the food industry will probably continue to decrease its reliance on sulfites as effective alternatives are found. As a result, the number of sulfited foods will decrease, and the sulfite residues present in sulfited foods will be diminished.

Key Contributors

Although numerous clinicians have identified cases and provided valuable clinical information, only a few groups are actively conducting research on the clinical, toxicological, and immunological aspects of sulfite sensitivity:

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