Sulfite Sensitivity — Unrecognized Threat: Is Molybdenum Deficiency the Cause?

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Sulfur dioxide and other so-called sulfiting agents as additives in foods and drugs may cause severe allergic reactions in susceptible individuals, especially asthmatics. The most widely used chemical preservatives, they have become a subject of increasing concern since 1976. The issue was recently brought to national attention by a CBS "60 Minutes" report on sulfite sensitivity aired twice in 1983.

"Sulfites" is a generic term for a group of compounds including sulfur dioxide, sodium sulfite, sodium and potassium bisulfite and sodium and potassium metabisulfite. They are antioxidants useful for their antimicrobial action and prevention of enzymatic and nonenzymatic discoloration (browning) of foods. Sulfites have been listed by the FDA as Generally Recognized as Safe (GRAS) for use in food, with a proviso, however, that they not be used in foods which are substantial sources of thiamine (vitamin Bl). Sulfites destroy thiamine. Currently, the Center for Science in the Public Interest, armed with data from Scripps Clinic and Research Foundation and other institutions, is applying pressure on the FDA to tighten restrictions.

Sulfite-Containing Foods

There is a history of use dating back to ancient Egypt and Rome when fumes of burning sulfur were used as a sanitizing agent in wine-making. The use of sulfur dioxide persists in several stages of wine-making today. Virtually all domestic and foreign wines and beers and many soft drinks contain the preservative. Sulfiting of other foods, particularly meats and fish, is centuries old but the popularity of salad bars in restaurants has probably brought consumption to an all-time high. Fruits and vegetables dipped in bisulfite look fresh and crisp and won't discolor even as they become stale. Restaurants also use them on shellfish and fried potatoes. Sulfur dioxide is used on virtually all dehydrated fruits and vegetables (eg. apricots, garlic powder) to preserve, color and flavor as well as to aid in the retention of ascorbic acid and carotene. Sulfites are commonly used in vinegar, pickles, relishes, olives and sauerkraut and in concentrates of bulk juices and purees such as tomato (eventually to be processed into consumer products). They are used in the processing of many food ingredients such as gelatin, beet sugar, corn sweeteners

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and food starches. There is no FDA restriction on use by food wholesalers, restaurants and groceries (with the exception of thiamine-containing foods). Only food processors are required to list sulfiting agents on package labels. Thus, sulfites in some fruit drinks and in commercial baked goods might appear on the label, but sulfites in tomato juice, sauces or pizzas prepared from bulk concentrates, probably would not.

Sulfite-Containing Drugs

Sulfites may be found in a number of parenteral medications within the following categories: antiemetics, cardiovascular preparations, antibiotics, psychotropic drugs, IV solutions, analgesics, anesthetics, steroids and nebulized bronchodilator solutions.

Some specific drugs among these product categories are: gentamycin ampoules, trimethoprim infusion, Bactrim infusion (trimethoprim and sulfamethoxazole), procaine injection (Novocaine), prochlorperazine ampoules (Compazine), morphine injection and promethazine injection (Phenergan).

Ironically, many of the drugs used to ease respiratory distress due to bronchospasm of asthmatics contain metabisulfite, viz. dexamethasone, epinephrine (Adrenalin), ethylnorepinephrine (Bronkephrine), isoetharine (Bronkosol), isoproterenol (Isuprel) and metaproterenol (Metaprel). Metoclopra-mide, commonly used to ease gastrointestinal distress of asthmatics and allergic individuals, also contains metabisulfite and life-threatening episodes of asthma after administration of this drug have been reported in both the major medical journal of America (Twarog and Leung, 1982) and Australia (Baker et al., 1981). Bronchospasm has been observed in asthmatics receiving nebulised gentamicin, and Dally et al. (1978) have suggested that the bisulphite preservative is responsible. Sulfite must be held suspect in any of the other medications known to cause bronchospasm. Further compounding the problem, patients cannot avoid sulfites and other additives to which they may be sensitive because they are considered an "inactive ingredient" and need not appear either on drug labels, in the accompanying literature, or the Physician's Desk Reference. The aforementioned list cannot therefore be considered complete, and the physician or patient must question the drug company before any inhalant, injection or I.V. medication is administered if sulfite sensitivity is suspected. As the wary gravida in Semmelweis' day, the asthmatic or allergic individual might do well to shun the hospital where sulfites abound in parenteral solutions. Although reports of life-threatening asthma attacks attributable to bisulfite in drugs are now appearing in the literature (Twarog and Leung, 1982 and Baker et al., 1981), we can only guess at the prevalence and severity of this newly discovered iatrogenic disorder.

Sulfur Dioxide in Air .

Another source of insult, other than food and drugs, to the sulfite-sensitive individual is sulfur dioxide in polluted urban air, and concentrations may be especially high on foggy days and in the vicinity of coal and oil-burning plants. In industrialized countries coal or oil-fired electric power plants account for 75 percent of the sulfur-oxide emission. The electric-power industry is proliferating rapidly and it is projected that such emission will increase several-fold by the year 2000.

Brief exposure to sulfur dioxide in concentrations of 5ppm or greater produces bronchoconstriction in most normal persons. Individuals with mild asthma, however, have a much lower threshold to sulfur dioxide and suffer bronchoconstriction at concentrations well below currently accepted standards for occupational exposure (Sheppard et al., 1980). A more recent report (Sheppard et al., 1981) provides data that moderate exercise increases the bronchoconstriction in asthmatics even further, thus reducing their level of tolerance to one-tenth their resting state level. Exercise itself has long been known to cause bronchoconstriction in persons with asthma, and so-called exercise asthma has been labeled "intrinsic asthma" as opposed to "extrinsic" or "allergic asthma" because the disease was not clearly related to exogenous allergens. Intrinsic or cryptogenic asthma also includes sufferers whose symptoms are triggered by such nonallergenic factors as infection, changes in barometric pressure or temperature, and emotional stress. In view of the newly established allergy to ingested sulfites, it will be interesting to see whether "exercise asthma" is in fact an allergy to

sulfur dioxide, hence another true "extrinsic asthma". It may be that asthmatic symptoms to very low levels in air are manifested only during exercise when there is a lower threshold of tolerance. Indeed, in support of such a thesis, Werth (1982) describes a case of sensitivity to inhaled but not ingested metabisulfite. A patient with a long history of exercise-induced asthma later observed similar symptoms upon ingestion of certain foods (notably dried apricots and Catawba grape juice, and less predictably, beer, wine, cheese, blueberries, apples and strawberries). Encapsulated metabisulfite had no effect but merely sniffing dried apricots brought on an attack. The author suggests that respiratory symptoms after ingestion of beer, wine, cheese and dried fruits, long assumed to be due to molds, may be metabisulfite sensitivity. Furthermore, inhaling chemicals such as metabisulfite in foods may provoke symptoms erroneously attributed to ingestion. Thus, some may do well to guard their noses against foods as well as against chimney stacks.

More Case Histories

The current controversy, which is forcing the FDA to review the GRAS status of sulfites and to impose new guidelines and stringent labeling, began with a case reported by Prenner and Stevens in 1976. The patient, a 50 year old male with no history of allergic rhinitis, asthma or eczema, experienced systemic allergic reactions, characterized as anaphylaxis, within minutes after eating in a restaurant. His treatment required emergency hospitalization. The agent responsible was identified as sodium bisulfite which produced classical wheal and flare reaction in a scratch test. With oral provocative challenge, signs and symptoms similar to those following the restaurant meal were produced. Since then, many other such incidents have surfaced, the most dramatic, reported in JAMA (Twarog and Leung, 1982), being of an asthmatic woman who experienced recurrent episodes of wheezing while eating restaurant meals. During one hospitalization she was treated with isoetharine (contains sulfite preservative) for mild wheezing, after which she experienced respiratory arrest. On a rehospitalization for wheezing and abominable pain she was again given isoetharine and again suffered respiratory failure from which she was rescued, only to succumb once more when treated with metoclo-pramide for her abdominal pain. The culprit was finally identified as bisulfite, an ingredient common to the restaurant fare, the isoetharine and the metaclopramide.

Common Symptoms

Symptoms which have been reported as commonly experienced by sulfite-sensitve individuals include: wheezing, labored breathing, chest-tightness, cough, faintness, extreme shortness of breath, respiratory arrest, loss of consciousness, blue discoloration of skin, flushing, angioedema, hives, laryngeal edema, hypotension, generalized itching, contact dermatitis, episodic swelling of hands, feet and eye areas, mood changes, clammy skin, abdominal cramps, nausea, diarrhea and anaphylactic shock.

Adverse Doses vs. Common Exposure

Tests show that 10-50 mg of oral and as low as 0.25 to 1 mg of inhaled sulfite elicit adverse reactions. The average daily consumption of most Americans is estimated at 2 to 3 mg/day and climbs to 5 to 10 mg/day for wine and beer drinkers. Restaurant patrons may consume 25 to 100 mg or more in one meal. These average doses are deceivingly low, for they include people who have only an occasional glass of wine or beer. (Since finished wines may have up to 350 ppm sulfite, a half bottle of wine alone may contain 125 mg and the salad bar, that much again!) According to a Monsanto Technical Bulletin, recommended levels of sulfur dioxide in dehydrated fruits and vegetables at Start of Storage may vary from a low of 200 to a high of 2000 ppm. This could amount to 56 mg in 1 oz of dried apricots so that a handful weighing 4 oz might contain over 200 mg of the preservative!

A typical therapeutic dose of Bronkosol (inhalation isoetharine) reported to have provoked an anaphylactic episode (Twarog and Leung, 1982) contains 1 mg sulfite. Bronkephrine (ethylnorepinephrine injection) and Adrenalin (epinephrine injection) contain between 1 and 2 mg bisulfite. The usual dose of Novocaine (procaine) injection may contain 100 mg of bisulfite!

As to sulfur dioxide in air, new findings show that normal individuals may develop bronchospasm at a sulfur dioxide level of 6

ppm and asthmatics at a level of only 1 ppm (Sheppard et al., 1980). Exercising asthmatics, however, will suffer at a level of 0.1 ppm (Sheppard et al., 1981), a concentration often exceeded in polluted urban air, let alone in industrial workplaces. Yet the Occupational Safety and Health Administration allows 5 ppm over an eight hour work shift. Since this is a time-weighted average, actual exposures will at times be considerably higher than 5 ppm.

Toxicity

Of the 20,000 some-odd chemicals, an estimated per capita consumption of 4 lbs. per year (Levantine and Almeyda, 1974), used in this country to preserve, color, stabilize, flavor, nutritionally enhance and otherwise modify foods and medications, sulfites have been considered among the safest. Sulfur dioxide and sulfites are oxidized in the body to sulfate, which is harmless, and excreted in the urine. It has generally been believed that this detoxification mechanism is adequate to handle the quantities that are likely to be ingested, so that for non-sensitive individuals, i.e. the majority of people, sulfites are still considered safe. But are they?

It has long been known that the aged and patients with bronchial asthma, chronic bronchitis and degrees of heart failure may suffer fatal consequences during periods of severe smog when the concentration of atmospheric sulfur dioxide is high. But even normal persons suffer bronchospasm at 5 ppm SO_2.

Reduced antibody formation was exhibited by rabbits exposed 80 days, $9^1/_2$ hours a day to a sulfur dioxide in air concentration of 36 mg/m^3 (Erban and Korinek, 1960). Since the Occupational Safety and Health Administration allows workers to be exposed year in and year out to 10 mg/m^3 as a time-weighted average (which seems uncomfortably close to the 36 mg/m^3 over 80 days) what must be the consequence to the immune system suffered by industrial workers and urban dwellers due to lower-level but chronic exposures?

Glucose tolerance tests have indicated disturbed carbohydrate metabolism in rabbits exposed to 50 - 100 ppm for two hours each day for up to six months (Sugawara, 1958). A possible disturbance of protein metabolism was also indicated in these rabbits. As far back as 1913, Rost and Franz reported that ingestion of 1 g of sodium sulfite per day decreased utilization of protein and fat in humans. Such studies have apparently not been repeated; hence we must question what the biochemical technology for discerning more subtle metabolic changes would reveal 70 years later about the effects of chronic, albeit low-level, exposure to sulfites. Sidorenkov (1957) has reported that inhaled sulfur dioxide readily penetrates into the blood stream from the lungs; therefore adverse findings on inhaled sulfur dioxide must carry over to ingested sulfites. He also finds a marked alteration in carbohydrate metabolism, perhaps due to the destruction of thiol groups of biologically active substances such as insulin. Reduction in liver glycogenesis and an increase in protein and non-protein nitrogen in the blood is also noted.

Perhaps the heartburn or indigestion many of us suffer after fancy wining and dining out may not be mere gluttony (surely we'd eaten that much at home before without consequence!) but due rather to the 0.007 oz (200 mg) of sulfite we may have ingested. 200 mg sulfite can make almost anybody vomit, according *to* Lafontaine and Goblet (1955) who induced the vomiting reflex in man consistently at such doses. And there are known additive effects when bisulfite is ingested together with other chemicals such as benzoic acid (Prenner and Stevens, 1976), another widely used preservative which also occurs naturally in some foods such as cranberries, cinammon and cloves.

Possible Cause of Sulfite Sensitivity

A possible explanation for sulfite sensitivity might be the widespread molybdenum deficiency which we find in a majority of our patients (Pfeiffer, 1983; Sohler, 1983). Many have no detectable blood molybdenum and most have levels below 5 ppb (normal 10 to 100 ppb). Molybdenum is the trace element contained in the enzyme sulfite oxidase which detoxifies sulfite to the inert and harmless sulfate.

Sulfite oxidase deficiency has been identified since 1967 as a rare inborn error of metabolism, and recently a new inherited disease due to deficiency of the "molybdenum cofactor", a constituent of the three

enzymes xanthine dehydrogenase, sulfite oxidase and aldehyde oxidase, has been recognized (Wadman et al., 1983). Neither of these genetic diseases responds to molybdenum supplementation, for here it is either the enzyme which is deficient or the metal in association with another moiety which is absent. Nonetheless, part of the patients' symptomatology is considered due to high accumulated toxic sulfite and insufficient sulfate. It is not inconceivable that some of the same symptoms may be evoked in normal individuals by simple molybdenum deficiency in the face of high environmental sulfite. Indeed Abumrad et al. (1981) have demonstrated that a molybdenum deficient diet would result in a sulfur handling defect at the level of transformation of sulfite to sulfate.

Molybdenum is contained in legumes such as soybeans, navy beans and lentils. This is gassy peasant food, so in developed countries these foods are avoided. Molybdenum is also available in Health Food stores in supplements of 150 to 500 mcg. A useful supplement to prevent sulfite effects would be 500 mcg AM and PM. In addition to molybdenum, it would also be prudent for the sulfite-sensitive individual, or for that matter for any individual exposed to undue quantities in foods, drugs or urban smog, to take additional supplements of vitamin C and thiamine, both known to be depleted by excessive sulfiting agents. Perhaps some pantothenic acid, found to have a significant protective action against sulfur dioxide poisoning (Hoetzel, 1961) would also be useful.

Discussion

Sulfiting agents are now considered to be the hidden trigger in up to five to ten percent of asthmatics or almost one million Americans. Though most cases of sulfite sensitivity occur in asthmatics, an untold number of others may be suffering as well. The FDA states that 30 percent of reported cases occurred in non-asthmatics with no known allergies.

In addition to this popular new issue of sulfite sensitivity, which is the impetus for the FDA review of sulfite status, we should perhaps consider simple toxicity anew. In this era of the salad bar, when vast amounts are being dumped into restaurant foods, and as sulfur dioxide in air ever increases, we may already be approaching or exceeding known toxic levels. And we have very little knowledge of the consequences of chronic low-level exposure particularly to the stressed individual with compromised detoxification mechanisms.

The mechanism of sulfite sensitivity remains obscure, some subjects exhibiting positive wheal and flare reactions to skin scratch tests and others reacting only to oral provocative or inhalation challenge. Even when sulfiting agents are definitely implicated, much more needs to be done to pin down the offending form or its route of entry. Reactions to sulfur dioxide in beverages, for example, occur so rapidly as to rule out intestinal absorption. It may gain access either by inhalation of the gas vaporizing from the solution or by absorption from the sublingual and the buccal mucosa. Reactions to metabisulfite in foods may actually be due to the liberation of SO_2 from acid foods.

Many patients previously thought to have food allergies or drug sensitivities or symptoms seemingly triggered by weather, exercise or stress may actually have been reacting to sulfites. Clinical appreciation of the presence of sulfite sensitivity is not only inherently difficult even for the astute diagnostician (Schwartz, 1983, states that the differential diagnosis includes functional bowel disease, anxiety, carcinoid and food allergy), but the majority of doctors are still ignorant of its very existence. It is therefore imperative that the physician and layman alike become enlightened on this subject and that individuals experiencing any of the symptoms listed above examine their habits and try to ascertain whether sulfite might be the culprit. Meanwhile, since we cannot totally manipulate our environment, sulfite-sensitive individuals as well as those suffering undue exposure would do well to fortify their diet with foods rich in molybdenum, vitamin C, thiamine and pantothenic acid or to take appropriate supplements. Sulfite sensitivity is difficult to diagnose and might be much more common than we suspect. We probably see but the tip of the iceberg.

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