Adverse reactions to sulfites

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Sulfites are widely used as preservatives in the food and pharmaceutical industries. In the United States more than 250 cases of sulfite-related adverse reactions, including anaphylactic shock, asthmatic attacks, urticaria and angioedema, nausea, abdominal pain and diarrhea, seizures and death, have been reported, including 6 deaths allegedly associated with restaurant food containing sulfites. In Canada 10 sulfite-related adverse reactions have been documented, and 1 death suspected to be sulfite-related has occurred. The exact mechanism of sulfite-induced reactions is unknown. Practising physicians should be aware of the clinical manifestations of sulfite-related adverse reactions as well as which foods and pharmaceuticals contain sulfites. Cases should be reported to health officials and proper advice given to the victims to prevent further exposure to sulfites. The food industry, including beer and wine manufacturers, and the pharmaceutical industry should consider using alternative preservatives. In the interim, they should list any sulfites in their products.

On utilise beaucoup les sulfites comme agents de conservation dans les industries alimentaire et pharmaceutique. Aux États-Unis on a rapporté plus de 250 cas d'effets nuisibles des sulfites, y compris choc anaphylactique, asthme, urticaire et oedème géant, nausée, douleurs abdominales et diarrhée, convulsions et même décès; 6 décès seraient reliés à la consommation de sulfite dans un restaurant. Au Canada on dénombre 10 cas, dont 1 mortel, où l'on soupçonne le rôle d'un sulfite. La pathogénèse de ces accidents est inconnue. Le praticien doit être au courant de leurs manifestations cliniques et savoir quels sont les aliments et les médicaments contenant des sulfites. On devrait rapporter aux autorités de santé des cas d'effets nuisibles des sulfites et, afin d'éviter l'exposition additionnelle, donner aux victimes des conseils adéquats. L'industrie alimentaire, y compris brasseries et établissements oenocoles, et l'industrie pharmaceutique devraient recourir à d'autres agents de conservation. D'ici là on devrait signaler la présence de sulfites sur les étiquettes.

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Sulfites are widely used in food processing to sanitize fermentation equipment and food containers, to reduce or prevent microbial spoilage of foods, to selectively inhibit undesirable microorganisms in fermentation industries and to prevent oxidative discolouration and nonenzyme browning during preparation, distribution and storage of food.[1-3] Apparently the earliest known use was in the treatment of wines with sulfur dioxide in Roman times.[4]

Six sulfiting agents have been listed by the United States Food and Drug Administration (FDA) as generally recognized as safe (GRAS) for use in food since 1959:[5-7] sulfur dioxide (SO_2), sodium sulfite (Na_2SO_3), sodium and potassium bisulfite ($NaHSO_3$ and $KHSO_3$), and sodium and potassium metabisulfite ($Na_2S_2O_5$ and $K_2S_2O_5$). The FDA allows the addition of sulfites to non-thiamine-containing foods and drinks without disclosure or other restrictions.[4,8] Rats maintained on diets providing adequate thiamine suffered no ill effects attributable to consumption of sulfites, up to 300 mg/kg per day.[4] Thiamine-deficient rats, however, showed toxic effects at doses as low as 50 mg/kg per day. Furthermore, although federal and state regulations prohibit the use of preservatives in ground beef, the addition of sulfites and other preservatives to ground beef to preserve the red colour has been common practice in the state of New York.[9]

Sulfites are used in restaurant foods to keep salad-bar vegetables and fruits looking fresh and to prevent browning in avocado dips. They are also used in seafood, potatoes, beer, wine, fruit drinks, baked goods and dried fruits and in the processing of some food ingredients, including beet sugar, corn sweeteners, food starches and gelatin.[3-8,10,11] In addition, many pharmaceuticals contain sulfites as antioxidants: they include bronchodilators, such as Alupent, Bronkosol, Isuprel, Micronefrin and Vaponefrin; injectable Adrenalin; local anesthetics, such as Novocain and Xylocaine; injectable corticosteroids, including Celestone, Decadron and Hydrocortone; injectable antibiotics, including Amikin, Garamycin and Nebcin; injectable antiarrhythmics, including Pronestyl; injectable lidocaine; analgesics, such as Demerol; antishock agents, including Aramine, Intropin and Levophed;

ophthalmic drops, including dexamethasone, Pred Mild, Pred Forte, prednisolone and sulfacetamide; and solutions for total parenteral nutrition and dialysis.[12-16]

In Canada manufacturers are required to disclose the presence of sulfiting agents in all manufactured foods and beverages except wine and beer. The maximum concentration of sulfiting agents allowed in various foods and drinks is shown in Table I.

The average person consumes 2 to 3 mg of sulfites per day. Wine and beer drinkers consume up to 10 mg/d. Restaurant foods may have the highest quantity, and those who eat in restaurants may ingest up to 150 mg/d.

Clinical manifestations

A level of sulfur dioxide as low as 1 part per million (ppm) may provoke airway obstruction in subjects with asthma.[17] However, it is reported that 0.1 to 0.6 ppm of sulfur dioxide may be generated during nebulization of bronchodilator solutions (e.g., Alupent, Bronkosol, Isuprel and Micronefrin).[18] In 1976 Prenner and Stevens[19] reported the first case of anaphylaxis following ingestion of sodium metabisulfite in a restaurant salad. Skin testing and passive transfer testing gave positive results, which suggested an IgE-mediated reaction. Subsequently it was reported that sulfur dioxide in orange drinks could induce asthma attacks.[20] In 1977 Stevenson and Simon[21] reported on four subjects with asthma who were sensitive to metabisulfites. Using single-blind provocative challenge testing with oral gelatin capsules containing lactose alone (placebo) or potassium metabisulfite in graduated doses of 1, 5, 10, 25 and 50 mg, they showed a significant decline in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in the subjects. The drop in FEV_1 and FVC was promptly relieved by an aerosol bronchodilator. Prick skin testing with potassium metabisulfite gave negative results. There was no peripheral basophil histamine release after the addition of metabisulfite at concentrations ranging from 10^{-2} *M* to 10^{-10} *M*. While these investigators could not find evidence of an IgE-mediated reaction, they postulated that activation of cholinergic reflexes could account for the clinical signs and symptoms in their four patients.

Sulfites were subsequently reported to produce a wide spectrum of severe adverse reactions, including anaphylaxis,[12,22] urticaria and angioedema,[23] asthma,[22,24,25] abdominal pain and diarrhea,[15] seizures[26] and death.[5,7,27]

Incidence

The exact incidence of sulfite sensitivity is not known. It has been estimated that 5% to 11% of people with asthma may be sensitive to metabisulfites;[7,28] thus, approximately 450 000 to 990 000 of the 9 million people with asthma in North America may be sulfite-sensitive.[7] It has recently been documented that 30% of the reported cases of sulfite sensitivity have been in people with no known history of asthma.[7] The exact incidence of sulfite sensitivity in the nonasthmatic atopic population and in the general population remains virtually unknown; further studies are required to explore this.

The FDA has received more than 250 reports of suspected sulfite-related reactions; as of February 1984 the FDA had received 6 reports of deaths allegedly associated with restaurant food containing sulfites.[27] In Canada 10 sulfite-related adverse reactions have been reported, and 1 death suspected to be sulfite-related has occurred (unpublished data, 1985).

Mechanism

The exact mechanism of sulfite-induced reactions remains unknown.[25] An IgE-mediated mechanism is suggested by the immediate onset of the reaction (e.g., anaphylaxis, bronchospasm, urticaria and angioedema, and rhinoconjunctivitis) and by positive results of scratch and intradermal skin testing with sodium bisulfite, 10 mg/mL, and passive transfer testing.[19] We reported on four patients[29] (one with anaphylaxis and three with asthma) who were found to be sensitive to potassium metabisulfite in single-blind provocative challenge testing according to the protocol of Stevenson and Simon.[21] Three of the four also had positive results of skin tests with potassium meta-

Table I—Maximum concentration of sulfites allowed in various foods and drinks in Canada (B.L. Huston: personal communication, 1984)

Food or drink	Concentration, parts per million (ppm)*
Fresh or prepared foods and dips in salad bars	Unlimited
Dried fruits and vegetables	2500
Apple or rhubarb jam, fancy, refiner's or table molasses, fig or pineapple marmalade with pectin, frozen sliced apples, fruit juices, gelatin, jelly with pectin, mincemeat, pickles and relishes, tomato paste, tomato purée	500
Unstandardized foods†	500
Beverages	100
Frozen mushrooms	90
Cider, honey, wine	70‡
Glucose, glucose syrup	40–400
Glucose solids, dried glucose syrup	40–150
Dextrose anhydrous, dextrose monohydrate	20
Ale, beer, light beer, malt liquor, porter, stout	15

*1 ppm = 1 mg/kg or 1 mg/L.
†Except those recognized to be a source of thiamine or unstandardized preparations of meat or meat by-products, fish, or poultry or poultry by-products.
‡In free state; 350 ppm in combined state as sulfur dioxide.

bisulfite, 1 mg/mL (one prick and two intradermal). Passive transfer testing gave positive results in both patients in whom it was carried out. Interestingly, when the serum from these two patients was heated to 56°C for 1 hour, passive transfer was not demonstrable, which suggested that an IgE-mediated mechanism was involved.

Another possible mechanism is stimulation of an orobronchial reflex — possibly due to inhalation of sulfur dioxide during swallowing or mouthwashing.[30]

More recently Jacobsen and colleagues[31] discovered that in sulfite-sensitive subjects with asthma, sulfite oxidase activity in fibroblasts may be reduced. Interestingly, cyanocobalamin (vitamin B_{12}), 1000 to 5000 μg taken orally, may fully or partially block the asthmatic response on challenge with metabisulfites.

Conclusions

Practising physicians should be aware of the clinical manifestations of sulfite-related adverse reactions. Single-blind provocative challenge testing with oral potassium metabisulfite carried out under close supervision by experienced specialists is necessary to confirm the diagnosis.[21,24,29] Physicians are urged to report documented sulfite-related adverse reactions to the Food Additives and Contaminants Section, Chemical Evaluation Division, Bureau of Chemical Safety, Health Protection Branch, Department of National Health and Welfare, Tunney's Pasture, Ottawa, Ont. K1A 0L2.

The ultimate question is, Should sulfites be banned? In the United States the National Restaurant Association (NRA) has advised its members, who operate 100 000 food service outlets, to stop using sulfites;[6,11,26] in June 1984 the NRA reported that only 4% of its members had continued to use sulfites.[27] The FDA has asked retail food establishments, including grocery stores and restaurants, to inform consumers by signs or notes that sulfiting agents have been used. In addition, the FDA has advised food processing companies, interstate conveyers and caterers that consumers must be notified if sulfites are used on foods that are eaten raw.[6]

It is now clear that sulfites are not safe preservatives.[11] Consideration should be given to using alternatives to sulfiting agents. Agents such as 1% to 2% citric acid can prevent browning of vegetables such as cauliflower, radishes and potatoes for up to 2 hours at room temperature. For long-term protection, 1% citric acid and 0.5% to 1% ascorbic acid can extend shelf life up to 7 days. One of the advantages of ascorbic acid is that it is a nutrient and thus would be favourably viewed by the consumer.[7] For economic reasons, citric acid and erythorbic acid could be used.[6,7] In the interim, for consumer protection the food industry, including wine and beer manufacturers, and the pharmaceutical industry should voluntarily list any sulfites in their products.

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to his practice and to his exercise routine over the next 6 weeks. Sequelae 15 months later included occasional slight loss of balance and low weight.

Discussion

Torten[1] noted the absence of a pathognomonic syndrome and the presence of misconceptions that hinder the diagnosis of leptospirosis in humans. Gutman and coworkers[2] emphasized this problem in their account of a patient with leptospirosis that was signalled by an ocular disorder. Avery[3] and Hart and colleagues[4] described the behavioural and social consequences of missed diagnoses, and Cheng[5] specified leptospiral arteritis as a major cause of cerebrovascular disease.

The use of rapid, accurate methods for detecting leptospires in blood and urine along with the IHA test for early antibodies can facilitate diagnosis. However, the immune response to leptospiral infection is highly variable, and, therefore, serologic testing alone should not be depended upon to establish the diagnosis. Culture of blood and urine samples with commercially available albumin–polysorbate-80 medium is now practical and should always be done in patients at risk of leptospirosis. Treatment with doxycycline is indicated because of its specificity, its ability to penetrate into the cerebrospinal fluid and the anterior chamber of the eye, and its long half-life (16 hours) in the body.[6]

The potential for exposure of Canadians to leptospiral infection increases with the amount of time spent with livestock. The risk of this debilitating disease, with its serious sequelae, merits much concern: public health authorities should obtain survey data, veterinarians should caution clients and coworkers and try to control the sources of infection, and the medical profession should recognize leptospirosis as a zoonosis indigenous to Canada.

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