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Adverse reactions to sulfites in drugs and foods

Sulfites are antioxidants that are used as preservatives in drugs and foods. Six sulfites have been listed as Generally Recognized and Safe (GRAS) by the Food and Drug Administration (FDA) for use in foods, and they are as follows: sulfur dioxide, sodium sulfite, sodium and potassium bisulfite and sodium and potassium metabisulfite. These antioxidants keep fruits and vegetables fresh looking, and because of this feature and the current increased popularity of salad bars in restaurants, increased ingestion of sulfites has occurred.

Metabisulfite reactions are important to dermatologists because of symptoms that involve the skin. The predominant skin lesion is severe flushing, but urticaria/angioedema, tingling, and pruritus have been reported. Besides flushing, the other major symptoms are acute bronchospasm and hypotension—one death has been reported to the FDA. The onset of these symptoms after an encounter with a particular substance is critical for the diagnosis to be suspected. The onset is extremely rapid, occurring between 2 to 15 minutes, depending on whether the sulfite is in the form of an inhaler, solution, capsule, or solid food particle. The first two forms result in a reaction within 2 minutes. Adverse reactions to aspirin, tartrazine, monosodium glutamate, and most food allergy occur at a significantly longer period of time, about 1 hour or more after ingestion.

The recognition and acceptance of metabisulfite reaction appears to be taking the slow course as in the early days of discovering and accepting the entity of tartrazine sensitivity, which was first discovered in 1959[1] and began to be accepted in 1967.[2–4] Similar to tartrazine, early manuscripts dealing with metabisulfite were not accepted for publication in many medical journals. Finally, they were accepted for publication in *Annals of Allergy*, presenting a strong case for preserving specialty publications.

When dissolved in an aqueous solution, sulfites generate SO_2, which may be the cause of, at least, some of the adverse reactions attributed to sulfites. Asthmatic patients are extremely sensitive to small concentrations of SO_2 gas and will respond with acute bronchospasm.[5,6] The first reported case[7] of an asthmatic patient dying of acute bronchospasm from SO_2 sensitivity probably occurred in 79 A.D., at the time of the eruption of Vesuvius. It seems that Pliny the Elder, a known asthmatic, was investigating this eruption when the smell of sulfur in the air caused him to stand in distress, and while leaning on two slaves, he suddenly collapsed and died. The two slaves with him survived. Reportedly, sulfur dioxide exceeds 20% of total active gases in most volcanic samples.

The frequency of sulfite sensitivity in an asthmatic population is estimated to be about 10%. These figures were approximated by obtaining data from Freedman[7] and using known information from epidemiology studies of aspirin and tartrazine. Freedman investigated 272 asthmatic patients

Table I. Reports of bisulfite reactions (adults)*

Investigators	Year	Patients		Positive bisulfite oral challenge	Symptom onset (min)	Positive bisulfite skin test	Remarks
		No.	Type				
Prenner and Stevens[9]	1976	1	Normal	Yes	Few	Yes	Pos P-K
Freedman[7]	1977	8	Asthmatics	Yes	1-2	ND	Pos smog
Stevenson and Simon[10]	1981	4	Asthmatics	Yes	10-15	Neg	Pos smog
Werth[11]	1982	1	Asthmatic	Yes	2	ND	Pos smog
Twarog and Leung[12]	1982	1	Asthmatic	Yes	2	Yes	Neg P-K
Schwartz[13]	1983	2	Asthmatics	Yes	10	Neg	
Habenicht et al[14]	1983	2	Normals	Yes (1)	15	ND	

ND: Not done; P-K: Prausnitz-Küstner reaction.

*From Settipane GA: N Engl Reg Allergy Proc 4:304, 1983.

and reported that thirty had adverse reactions to a soft drink that contained both tartrazine and sulfites. Since approximately 10% of asthmatics have aspirin intolerance and about 10% of this subgroup also have tartrazine sensitivity, the extrapolation of these figures results in the approximation that twenty-seven (10%) of Freedman's 272 asthmatics had adverse reactions to sulfites. A recent report[8] stated that 8.2% of asthmatic patients without a suggestive history had positive metabisulfite challenges.

In the modern literature in which a positive challenge was used to establish the diagnosis, Prenner and Stevens[9] were the first to report, in 1976, that bisulfite caused a severe adverse reaction in an asthmatic patient. In 1977, Freedman[7] reported that eight asthmatic patients had severe reactions to bisulfites. In 1981, Stevenson and Simon[10] reported four bisulfite cases, followed by other reports in rapid succession: Werth,[11] Twarog and Leung,[12] Schwartz,[13] and Habenicht et al[14] (Table I).

Although the FDA has received reports of over ninety cases of adverse reactions, only about one third of these cases have been published in the medical literature. Most of the patients reported in the medical literature had a prior history of asthma. All had a positive oral challenge to bisulfite, and all had reactions within 15 minutes from challenge. In only two of these reports, positive skin tests to bisulfite were found.

One of these reports also demonstrated a positive Prausnitz-Kustner (P-K) reaction, while the other report stated that the P-K reaction was negative. In four reports, asthmatic patients not only reacted to bisulfites in foods, but also reacted to inhaled bisulfites or to smog (SO_2), demonstrating the strong relationship between bisulfites and SO_2. It is apparent that a significant number of these asthmatics with bisulfite sensitivity have negative allergy skin tests and, therefore, are nonatopic in nature.[10,12] The lack of IgE mechanism is confirmed by the finding that normal IgE, total eosinophil count, and histamine levels were observed during acute reactions.[12]

The pathogenic mechanism of bisulfite reaction appears to be through neural reflex actions, involving the irritant receptors in the nose and upper airways, with the vagus nerve being the main efferent pathway. Atropine inhibits the bronchospasm induced by SO_2.[5,6] Stimulation of the parasympathetic system may also account for pruritus, urticaria/angioedema, as well as gastrointestinal and cardiovascular complaints. The rapid onset of symptoms and absent allergic markers add credence to this neurogenic theory. Freedman,[7] Stevenson and Simon,[10] and Werth[11] also have mentioned this reflex action as a possible mechanism among other theories. An overall view of all reports appears to make the neurogenic theory the most likely mechanism.

A major aim of this editorial is to list medications that contain the preservative bisulfite (Table II). Most of these medications were obtained by

Table II. Drugs that contain sulfites

I. Bronchodilator inhalant solutions
- Alupent (metaproterenol sulfate)
- Bronkephrine (ethylnorepinephrine HCl)
- Bronkosol (isoetharine HCl)
- Isuprel hydrochloride solution (isoproterenol HCl)
- Metaprel (metaproterenol sulfate)
- Micronefrin (racemic epinephrine)

II. Tablets
- Isuprel HCl Glossets (isoproterenol HCl)

III. Injectables
- A. Adrenalin 1/1,000 (epinephrine)
  - Aldomet Esther HCl injection (methyldopate HCl, MSD)
  - Aramine (metaraminol bitartrate)
  - Celestone phosphate (brand of metamethasone sodium)
  - Compazine (prochlorperazine)
  - Decadron-LA suspension (dexamethasone acetate)
  - Decadron phosphate injection (dexamethasone sodium phosphate)
  - Decadron phosphate with Xylocaine (dexamethasone sodium phosphate and lidocaine HCl)
  - Dopastat (dopamine HCl)
  - Intropin (dopamine HCl)
  - Isuprel HCl sterile injection 1:5,000 (isoproterenol HCl)
  - Largon (propiomazine HCl)
  - Levophed bitartrate (norepinephrine bitartrate)
  - Levoprome (methotrimeprazine)
  - Lidocaine HCl with epinephrine
  - Marcaine HCl with epinephrine (bupivacaine HCl and epinephrine)
  - Mepergan (meperidine and promethazine HCl)
  - Nesacaine (chloroprocaine HCl)
  - Nesacaine-CE (chloroprocaine HCl)
  - Novocaine (procaine HCl injection [U.S.P.])
  - Nubain (nalbuphine HCl)
  - Phenergan (promethazine HCl)
  - Pronestyl (procainamide HCl)
  - Reglan (metoclopramide HCl)
  - Serpasil (reserpine USP)
  - Thorazine (chlorpromazine HCl)
  - Tofranil (imipramine HCl [U.S.P.])
  - Torecan (brand of thiethylperazine [U.S.P.])
  - 10% Travasol (amino acid) injection without electrolytes
  - Trilafon (brand of perphenazine [U.S.P.])
  - Tubocurarine chloride injection (U.S.P.)
  - Yutopar (ritodrine HCl)
- B. Antibiotics
  - Amikin (amikacin sulfate)
  - Bactrim IV infusion (trimethoprim and sulfamethoxazole)
  - Bristagen (gentamicin sulfate)
  - Gantrisin (sulfisoxazole)
  - Garamycin injectable (gentamicin sulfate)
  - Kantrex injection (kanamycin sulfate injection)
  - Nebcin (tobramycin sulfate)
  - Septra IV infusion

IV. Miscellaneous
- Cortisporin otic solution (polymyxin B-neomycin-hydrocortisone)
- Decadron in ocumeter (dexamethasone sodium phosphate)
- Decadron phosphate–0.1% sterile ophthalmic solution (dexamethasone sodium phosphate)
- Neodecadron sterile ophthalmic solution (neomycin sulfate–dexamethasone sodium phosphate)
- Otocort ear drops
- Pred-forte ophthalmic suspension
- Pred-mild ophthalmic suspension
- Propine ophthalmic solution (dipivefrin HCl)

our review of *Physicians' Desk Reference*, and some were obtained from published reports.*,[12,15] These medications should be used with caution in asthmatic patients and should not be used in those with a known history of sulfite or SO_2 sensitivity.

Foods that contain bisulfite have been adequately described by Twarog[16] and others.[10–14,17] These foods are listed in Table III. It has been estimated that the average U.S. diet contains about 2 to 3 mg of sulfite daily. However, a restaurant meal may contain 20 to 200 mg of sulfites as preservatives.

Besides avoidance, preventive treatment for these sulfite-sensitive patients is based on a recent report by Jacobsen, Simon, and Singh.[18] They demonstrated that these patients have a deficiency of the enzyme sulfite oxidase. Also, they reported that cyanocobalamin (vitamin B_{12}) can serve as an extracellular, nonenzymatic catalyst for the oxidation of sulfites in these deficient individuals. When given as an oral dose of 1 to 5 mg preceding sulfite challenge, vitamin B_{12} offers excellent pro-

*Washington Drug Letter, April 4, 1983.

Table III. Sulfites in foods

Restaurant salads and fresh fruits
Vegetables wrapped in cellophane
Dried fruits (e.g., apricots)
Potato (e.g., French fries and potato chips)
Avocados
Wine and vinegar
Beer
Cider
Some fruit drinks (especially outside U.S.A.)
Baked products
Gelatin
Beet sugar
Corn sweeteners
Food starches
Shrimp
Sausage meats (outside U.S.A.)

tection to these patients. Other drugs that are able to prevent clinical sulfite reactions as shown in challenge studies are atropine, cromolyn, and doxepin.[19]

The FDA and state health departments have initiated steps in alerting consumers to the possible dangers of bisulfites and in getting producers to identify these chemicals in their packages. However, bureaucratic processes are slow, and it is up to the physician to demonstrate leadership in prescribing medications and educating patients.[20]

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