Asthma and Anaphylactoid Reactions to Food Additives

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SUMMARY

Presumed allergic reactions to hidden food additives are both controversial and important. Clinical manifestations include asthma, urticaria, angioedema, and anaphylactic-anaphylactoid events. Most adverse reactions are caused by just a few additives, such as sulfites and monosodium glutamate. Diagnosis is suspected from the history and confirmed by specific challenge. The treatment is specific avoidance.

RÉSUMÉ

Les présumées réactions allergiques aux additifs alimentaires font l'objet de controverses mais sont importantes. Parmi les manifestations cliniques, on note l'asthme, l'urticaire, l'angio-oedème et les incidents anaphylactiques-anaphylactoïdes. La plupart des réactions indésirables sont causées par un petit nombre d'additifs, tels les sulfites et le glutamate monosodique. On peut soupçonner ce diagnostic à l'histoire et le confirmer par des tests de provocation spécifiques. Le traitement consiste à éviter l'agent casual.

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NUMEROUS AGENTS ARE ADDED to the food we eat: colouring agents, preservatives, antioxidants, flavouring agents, stabilizers, sweeteners, thickening agents, and so on. Only a few of these agents are currently known to play a role in precipitating allergiclike reactions (typically urticaria, angioedema, asthma, and anaphylaxis).

The mechanism of the reaction caused by the best-studied ingested food additives (sulfites, monosodium glutamate, tartrazine, and benzoates) remains unknown, although certain agents, such as gums, can clearly cause a typical immunoglobulin E (IgE)-mediated allergic response. This article discusses the clinical features, diagnosis, and management of asthma, urticaria, and anaphylactic responses caused by common food additives (*Table 1*[1]).

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Sulfites

Sulfiting agents are used mainly as antioxidants in food fresheners and to control microbial growth in fermented beverages (*Table 2*). Studies have suggested that 5% to 10% of asthmatic patients experience an exacerbation of their asthma within 10 to 20 minutes of ingesting sulfites.[1-4] Severity of reaction ranges from mild symptoms after ingesting a large amount to life-threatening responses after ingesting small amounts.[5,6] The response most commonly manifests as asthma alone but can include flushing, urticaria, angioedema, tearing, runny nose, abdominal pain, seizures, and anaphylaxis.[1-4,7,8] Extremely sensitive patients have died from such responses.[1-4]

Sulfites in foods or drinks can be present as sulfur dioxide, sodium sulfite, sodium or potassium metabisulfite, and sodium or potassium bisulfite. Sulfites were commonly used in restaurants to keep salads and uncooked vegetables looking crisp and fresh. However, after one sulfite-related death in Canada, this use was banned. Sulfites can still be used as a whitener for potatoes, grapes, and shrimp. Legislation requiring the nature and concentration of sulfite to be labeled is expected. Today, the most common sources of

sulfites are beer, wine, dried apricots, other dried fruit, frozen french fries, frozen seafood, jams, jellies, and bottled fruit juices.

The mechanism of the asthmatic response to sulfites is unknown. A few sulfite-sensitive patients have positive skin test results to metabisulfite and a positive Prausnitz-Küstner reaction (passive transfer), suggesting an IgE-mediated allergic reaction.[1-7] Another proposed mechanism is a local response to released sulfur dioxide or sulfite inhalation, as asthmatics have been shown to be particularly responsive to the irritant bronchoconstrictor effect of inhaled sulfur dioxide.[9-12] However, studies have indicated no clear relationship between inhaled sulfur dioxide, airway responsiveness, and ingested sulfite sensitivity, suggesting that other factors also play a role in the response. Sulfite oxidase deficiency has been identified by fibroblast tissue cultures in sulfite-sensitive patients. Such a deficiency could delay clearance of a sulfite load and magnify the effect of sulfites.[13]

Table 1. **Common food additives known to cause adverse reactions**

ADDITIVE	REACTION
Sulfites	Asthmatic attack
	Anaphylaxis
	Abdominal pain
	Urticaria and angioedema Rhinoconjunctivitis
	Seizure
	Death
Monosodium glutamate	Chinese restaurant syndrome Late and immediate onset asthma
Benzoates, butylated hydroxytoluene, butylated hydroxyanisole	Chronic urticaria
Tartrazine	Asthma Urticaria
Nitrites, nitrates	Gastrointestinal complaints Cyanosis
Aspartame	Urticaria and angioedema

Adapted from Yang.[1]

Some multidose bronchodilator solutions for aerosolization previously contained sulfites as preservatives but no longer do. Freon-propelled inhalers do not contain sulfites. Some injectable solutions, such as epinephrine, do contain sulfites as preservatives, but the amount injected has not been shown to precipitate asthma or anaphylactoid responses.[14]

Sulfite sensitivity should be suspected if a patient's history indicates asthma exacerbation within 20 minutes of ingesting foods or beverages. If a definitive diagnosis is necessary, single- or double-blind challenge testing can be carried out.[1-6] This carries some risk and is contraindicated in patients with a history of very severe response. It should be performed only in a hospital with staff and facilities for resuscitation in the event of a severe reaction, and with the patient's informed consent. As with any challenge of food additives (*Table 3*), a control day with placebo challenge is required (using lactose or, if the patient is lactose intolerant, xylose). The patient should avoid sulfite-containing foods for at least 5 days before challenge.

The challenge should consist of repeated increasing doses of potassium metabisulfite administered at intervals depending on the timing of symptoms recorded in the history (generally every 20 minutes). Powdered metabisulfite or placebo is dissolved in 10 mL of water or juice, and the patient is asked to hold the solution in his or her mouth for 30 seconds before swallowing it. Increasing doses of metabisulfite (eg, 1 mg, 5 mg, 15 mg, 45 mg, 100 mg, or smaller increments in those with severe symptoms) are used for challenge, and the response is monitored by spirometry before, and 20 minutes after, each dose. If the forced expiratory volume in 1 second, or FEV_1, falls 20% or more, the challenge is stopped for the day, and the patient is monitored until clinically improved. An FEV_1 that falls as much as, or more than, 20% more than on the placebo day indicates a positive response to sulfites. Medication use should be consistent both days; guidelines for discontinuing medications should be followed as in other challenges (*Table 3*).

Treatment is by avoidance and patient education on the appropriate management of symptoms caused by inadvertent

ingestion (using a prepared adrenalin syringe or going to a hospital emergency department).

Monosodium glutamate

Monosodium glutamate (MSG) is added to food to enhance flavour. It is present most frequently in Chinese restaurant food and is also in commercially prepared soups, stews, and other main dishes in quantities of up to 5 g per portion.

The most common manifestation of MSG sensitivity (Chinese restaurant syndrome)[15,16] occurs 1 to 2 hours after MSG ingestion and is characterized by headache, nausea, sweating, chest tightness, burning, and numbness. Occasionally, severe symptoms mimic angina. Asthma exacerbations have been documented rarely but can occur up to 12 hours after MSG ingestion.[17,18] Sensitivity to MSG appears to be far less common clinically than sulfite sensitivity. The mechanism is unknown, but the symptoms could be caused by stimulation of irritant receptors in the airways or by a central effect.

If the diagnosis is suspected from the history, a trial of MSG avoidance and specific oral challenge testing can be done. Either MSG (in doses ranging from 500 mg to 3 g) or lactose placebo are given by capsule. The challenge procedure is similar to that for sulfites with a placebo control day, patient blinding, and consent. However, the follow-up time after each dose could be several hours, depending on the timing of previous presumed reaction to MSG noted in the history.

Tartrazine and benzoates

Tartrazine is a yellow dye used in some yellow, orange, and green colours for foods, drinks, and medications. Benzoates are used as preservatives in jams, jellies, pickles, and soft drinks. Studies have reported that these additives exacerbate asthma, urticaria, and angioedema, particularly in acetylsalicylic acid–sensitive asthmatics (8% to 44% in some studies).[19-22] However, studies during the past 12 years with double-blind challenge testing have shown only rare patients to be truly sensitive to these agents.[23] Thus, an avoidance diet is unjustified for ASA-sensitive asthmatics unless carefully compared with a normal diet by peak flows, symptom scores, and medication requirements. Apparent improvements with avoidance should be documented by single- or double-blind challenges as described for the other additives before placing patients on long-term, very restrictive diets.

The mechanism of the response is unknown, but tartrazine and benzoate have been reported to stimulate lymphocyte-derived and leukocyte inhibitory factors, suggesting a possible role for cell-mediated immunity.[24]

Other ingested food additives

Other food additives, such as spices and gums, can cause IgE-mediated events as in true food allergy (urticaria, angioedema, asthma, or anaphylaxis). When an allergy history suggests reactions to foods containing such agents, skin testing and, where needed, single- or double-blind oral challenges can be helpful.

Aspartame has been reported to precipitate urticaria in a few patients, but to date this has not been proved by double-blind challenge.[25-27]

Antimicrobial drugs

Health and Welfare Canada[28] has limited the allowable levels of almost all antibiotics found in milk, poultry, and meat. Although these levels are extremely low (0.01 to 4 ppm maximum residue), they could be responsible for IgE-mediated allergic reactions in susceptible individuals. Patients with suggestive histories should undergo appropriate investigations (skin tests or challenge).

Inhaled food additives

In addition to ingested food additives, inhaled food additives, especially among food-industry workers, can cause or exacerbate rhinitis, conjunctivitis, and asthma. Examples include enzymes, such as fungal amylase used by bakers and in flour manufacture; papain used as a meat tenderizer[29]; sulfites used to make frozen french fries; and pectin used in jam production.[30] Patients who inhale food additives at work may have a history of exacerbation of symptoms during the week with improvement on weekends and holidays.

Investigations should include documentation of a work relationship by serial

They have not realized that those studies showing a rare effect tested patients ON meds with a SMALL amount of dye. Oh yeah - and often they had not even first avoided the dye!!

avoiding tartrazine & other food dyes is sensible not "restrictive"

see note top of next parag

Table 2. **Common sources of food additives**

SULFITES
- Wine
- Beer
- Salad bars
- Frozen french fries
- Dried fruit, eg, apricots, white raisins
- Lemon concentrates for cooking or drinks
- Some baked goods

MONOSODIUM GLUTAMATE
- Chinese meals
- Soups
- Stews

TARTRAZINE
- Jams
- Some butter
- Candies
- Cakes
- Tablets

BENZOATES
- Some soft drinks
- Pickles
- Jams
- Jellies
- Cakes

peak flow recordings and repeat measurements of airway responsiveness at work and off work; skin testing where feasible (eg, with inactivated papain); and, if needed, specific inhalation challenge in a specialized unit. Treatment, after establishing the diagnosis, is again by avoidance.

Table 3. **Food additive oral challenges**

CHALLENGES
• Trial of avoiding the specific additive should show improvement.
• Single- or double-blind challenge testing can be performed.
• Placebo-control day (lactose or, if lactose intolerant, xylose) is required.
CONDITIONS
• If possible, inhaled bronchodilators should be stopped at least 8 hours before each challenge and long-acting theophylline for 48 hours. Cromolyn and nedocromil should be stopped before sulfite challenge.
• Spirometry should be assessed before and at intervals after each dose and the challenge stopped if FEV_1 falls 20% or more. Baseline FEV_1 must be at or greater than 1.5 L or 70% of best.
• Timing between doses is assessed from the history of symptom onset after ingestion.
• Challenges should be performed in hospital with informed consent and facilities for resuscitation.
• A positive challenge is a 20% or more fall in FEV_1 after ingesting the additive compared with the placebo control day.
CONSIDERATIONS
• Consider sulfite sensitivity in patients with intermittent acute exacerbations of asthma within 20 minutes of ingesting wine, beer, dried fruit, or restaurant meals.
• Consider a possible exacerbating role for MSG, tartrazine, and benzoates in patients with severe asthma, urticaria, and angioedema, even without clear, food-related symptoms. An additive avoidance trial might be worthwhile if carefully monitored.
• Before restricting a patient to long-term additive avoidance, carefully document the effects of additive avoidance compared with normal diet by assessing peak flows, symptoms, and medication needs in the absence of other confounding variables.

Conclusion

Food additives should be considered as possible triggering factors among patients with asthma, urticaria, angioedema, or anaphylaxis. During history-taking all patients should be asked whether meals or drinks appear to precipitate symptoms. If symptoms appear to be provoked by several different foods or drinks, the possibility of a common food additive should be considered and further investigated. A trial of additive avoidance can be used, but it should be carefully monitored and compared with symptoms during a similar period on a normal diet. Blinded challenges can also be helpful. Inhaled food additives should be considered among food workers with symptoms of allergy suggestive of occupational exposure. ■

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References

1. Yang WH, Purchase ECR, Rivington RR. Positive skin tests and Prausnitz-Küstner reactions in metabisulfite sensitive subjects. *J Allergy Clin Immunol* 1986;78:443-9.
2. Yang WH, Purchase ECR. Adverse reactions to sulfites. *Can Med Assoc J* 1985;133:865-8.
3. Yang WH. Adverse reaction to food and food additives. *Allergy* 1989;19:7-20.
4. Dalton-Bunnow MF. Review of sulfite sensitivity. *Am J Hosp Pharm* 1985;42:2220-6.
5. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol* 1981;68:26-32.
6. Stevenson DD, Simon RA. Sulfites and asthma. *J Allergy Clin Immunol* 1984;74:469-72.
7. Prenner BM, Stevens JJ. Anaphylaxis after ingestion of sodium bisulfite. *Ann Allergy* 1976;37:180-2.
8. Schwartz HJ. Sensitivity to ingested metabisulfite: variations in clinical presentation. *J Allergy Clin Immunol* 1983;71:487-9.
9. Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980;122:873-8.
10. Bethel RA, Epstein J, Sheppard D, Nadal JA, Boushey HA. Sulfur dioxide induced bronchoconstrictor in freely breathing, exercising, asthmatic subjects. *Am Rev Respir Dis* 1983;128:987-90.
11. Delohery J, Simmul R, Castle WD, Allen DH. The relationship of inhaled sulfur dioxide reactivity to ingested metabisulfite in patients with asthma. *Am Rev Respir Dis* 1984;130:1027-32.
12. Schwartz HJ, Chester EH. Bronchospastic responses to aerosolized metabisulfite in asthmatic subjects: potential mechanisms and clinical implications. *J Allergy Clin Immunol* 1984;74:511-3.

13. Jacobsen DW, Simon RA, Singh M. Sulfite oxidase deficiency and cobalamin protection in sulfite sensitive asthmatics (SSA)[abstract]. *J Allergy Clin Immunol* 1984;73:135.
14. Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984; 74:623-30.
15. Kwok RHM. Chinese restaurant syndrome [letter]. *N Engl J Med* 1968;278:796.
16. Schaumburg HH, Byck R, Gerstl R, Mashman JH. Monosodium L-glutamate: 1+5 pharmacology and role in the Chinese restaurant syndrome. *Science* 1969;163:826-8.
17. Allen DH, Baker GJ. Chinese restaurant asthma. *N Engl J Med* 1981;305:1154-5.
18. Allen DH, Delohery J, Baker G. Monosodium L-glutamate induced asthma. *J Allergy Clin Immunol* 1987;80:530-7.
19. Settipane GA, Pudu-Pakkam RK. Aspirin intolerance. III. Subtypes, familial occurrence and cross reactivity with tartrazine. *J Allergy Clin Immunol* 1975;56:215-21.
20. Tarlo SM, Broder I. Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clin Allergy* 1982; 12:303-12.
21. Stenius BSM, Lemola M. Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clin Allergy* 1976; 6:119-29.
22. Spector LS, Wargaard CM, Farr RS. Aspirin and concomitant idiosyncracies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64:500-6.
23. Stevenson DD, Ouimon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986;78:182-91.
24. Warrington RJ, Sander PJ, McPhillips S. Cell mediated immune responses to artificial food additives. *Clin Allergy* 1986;16:527-33.
25. Kulcyzchi A. Aspartame-induced urticaria. *Ann Intern Med* 1986;104:207-8.
26. Garriga MM, Berkbile C, Metcalfe DD. A combined single blind, double blind, placebo controlled study to determine reproducibility of the hypersensitivity response to aspartame. *J Allergy Clin Immunol* 1991;87:821-7.
27. Geha R, Buckley CE, Patterson R, Polmar S, Saxon A, Rohr A, et al. Aspartame is no more likely than placebo to cause allergic reactions [abstract]. *J Allergy Clin Immunol* 1992;89:184.
28. Health and Welfare Canada. *Food and Drugs Act and Regulations*. Ottawa: Health and Welfare Canada, April 11, 1991:Table III, Section 15.
29. Flindt MLH. Allergy to alpha-amylase and papain. *Lancet* 1979;1:1407-8.
30. Cohen A, Forse M, Tarlo S. Occupational asthma caused by pectin inhalation in the manufacture of jam. *Chest* 1993;103:309-11.

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