

Hypersensitivity reactions to food additives

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Purpose of review

To provide an updated concise review on food additives adverse reactions, diagnosis, and management.

Recent findings

Despite the common use of food additives, their adverse reactions seem to be very rare in the general population (0.01–0.23%) but higher in atopic individuals (2–7%).

Probably because of the difficulty in diagnosis, most of the available information is based on case reports or small series. Reported reactions are mostly mild and may affect the skin, the gastrointestinal tract, or the airways, and rarely anaphylaxis.

Summary

Food additives should be suspected as the culprit in patients who report a history of reactions to a number of unrelated foods or to a certain food when commercially prepared but not when prepared at home. The major problem in dealing with reactions to additives is the identification of the offending agent(s). Apart from a careful history taking, allergy skin testing or in-vitro testing are rarely useful. Trials of elimination and reintroduction may be more helpful. If the anticipated reaction is severe, a well designed challenge testing should be carried out. Once the offending additive(s) is confirmed, treatment is avoidance. Because accidental exposure often happens, patients with a history of severe reactions should have self-injectable epinephrine and wear MedicAlert (Turlock, California, USA) identification.

Keywords

additives, food additives, food allergy, food dyes, food hypersensitivity, food intolerance, food preservatives

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Introduction

Food additives are substances added to food at any stage of its production, processing, treatment, packaging, transportation, or storage. Thousands of additives, either synthetic or natural, are used worldwide. Historically, additives were primarily of natural origin, then synthetic additives were gradually introduced and became predominant. The recent interest in 'natural' products has been associated with more use of substances derived from plants, insects, and animal origin. Because of their protein content, natural additives are more likely to induce immune-mediated adverse reactions. In the United States, the Food and Drug Administration (FDA) maintains an online updated list of more than 3000 food additives with relevant administrative and chemical information [1]. This review provides information on various additives and their uses in food preparations, and the reported relevant adverse reactions. Provided also is a diagnostic approach on how such reactions can be suspected and the offending additive can be identified and avoided.

Prevalence

Most of the reports of adverse reactions attributed to additives were case reports, small series, or based on poorly controlled challenge testing. There is a notable shortage of large, well designed, double-blind studies with defined criteria. Hence, there is lack of consensus regarding the prevalence and the clinical manifestations. Contrary to the general public perception, the prevalence seems to be rather low. Studies in Denmark estimated the prevalence at 1–2% in atopic children [2]. In another group of children with atopic diseases, reactions to food additives occurred in 7% by open challenge and in 2% by blind challenge [3]. In a large British survey of more than 15 000 individuals, the estimated prevalence of self-reported symptoms to food additives was 0.01–0.23% [4]. On the contrary, in 54 patients with various allergic diseases and suspected of having reactions to food additives, double-blind challenge testing with seven common additives showed no statistically significant difference between food additives and placebo [5**].

Food additive uses and reactions

Food additives are widely used for various purposes with marked geographic variations. Common examples are listed in Table 1 [6] according to their common use. The reported reactions varied widely according to the type of population studied and the criteria. They encompassed skin rashes, respiratory symptoms, gastrointestinal symptoms, and in rare occasions, systemic anaphylaxis.

Antioxidants

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are common antioxidants that preserve fat

Table 1 Classification of food additives and common examples

Antioxidants	BHA BHT Propyl gallate Tocopherols
Stabilizers	EDTA Gums (e.g. carrageenan, guar, and others) Waxes
Emulsifiers	Gums (e.g. Arabic, karaya, and tragacanth) Lecithin Propylene glycol
Flavorings and taste enhancers	MSG
Spices	Aniseed Cinnamon Coriander Cumin Fennel Flaxseed Ginger Hops Mustard Nutmeg Red pepper White pepper
Artificial sweeteners	Aspartame (Equal, NutraSweet) Saccharin (Sweet 'N Low) Sucralose (Splenda, Sorbitol)
Natural sweeteners	Corn syrup Fructose Glucose Sucrose
Preservatives and antimicrobials	Benzoates Citric acid Nitrates and nitrites Parabens Salicylates Sorbic acid Sulfiting agents
Dyes	
Blue	Brilliant blue, indigo carmine, and patent blue
Green	Chlorophyll and fast/patent green
Orange	Annatto ^a and sunset yellow
Red	Allura red, amaranth, carmine ^a , erythrosine, and ponceau
Yellow	Quinoline yellow, saffron ^a , tartrazine, turmeric, and curcumin

BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; EDTA, ethylenediaminetetraacetic acid; MSG, monosodium glutamate. Modified from Wilson and Bahna [6].

^a Natural dyes.

and slow spoilage. These are used commonly in butter, cereals, chewing gum, baked goods, snack foods, dehydrated potatoes, and beer. In 100 patients with chronic urticaria, provocation tests with various food additives such as azo dyes, benzoates, BHT, BHA sorbic acid, quinoline yellow, carotene, canthaxanthine, annatto, and nitrite revealed one or more positive reactions in one-third of the patients [7]. BHA and BHT have been identified as the trigger for exacerbations in a case report [8] of two patients with chronic urticaria. We did not encounter a study on the estimated prevalence of this problem.

Food dyes

Of numerous synthetic food dyes, nine are certified and approved by the FDA for use by the food industry in the United States. Certified dyes include FD&C blue nos. 1 and 2, FD&C green no. 3, FD&C red nos. 3 and 40, FD&C yellow no. 5 (tartrazine) and 6, orange B, and citrus red no. 2. Natural colorings, such as annatto, carmine and saffron, have been associated with IgE-mediated hypersensitivity reactions.

Annatto is yellowish orange and is obtained from the seeds of tropical tree *Bixa orellana*. It is used particularly in cheddar cheese, ice cream, and beverages. It has been reported as an occasional cause of urticaria and even anaphylaxis. Using annatto extract dose equivalent to the amount used in 25 g of butter, oral challenge of 56 patients with chronic urticaria, angioedema, or both was positive in 26% of patients within 4 h [9]. Carmine is a common red dye derived from the cochineal insect and commonly used in products such as juices, ice cream, yogurt, and candy. Wüthrich *et al.* [10] have reported five cases of IgE-mediated anaphylactic reaction to carmine, with positive skin prick testing (SPT) and specific IgE.

Tartrazine is a synthetic yellow azo dye obtained from coal tar. It is one of the least expensive synthetic colors and most commonly used in confectionery, cotton candy, soft drinks, instant puddings, cake mixes, jam, jelly, gelatins, mustard, and many convenience foods. In rare cases, tartrazine has been a trigger of urticaria or asthma. Well designed challenge testing showed that confirmed reactions are much less than what is usually claimed. A recent Cochrane meta-analysis [11] was inconclusive on the role of tartrazine in asthma. In 10 asthmatic children who gave a history of cough or wheeze after orange drinks, blind oral challenges with tartrazine 1 mg caused significant increase in bronchial reactivity in four children as determined by histamine bronchial provocation [12]. There is a general belief of cross-reactivity between tartrazine and acetylsalicylic acid, but the reports are inconsistent. A single-blind oral tartrazine challenge [13] with up to 50 mg in 194 patients with aspirin-sensitive asthma caused an attack in seven patients, but repeated double-blind challenges in six were negative.

The test was negative in 43 asthma patients who tolerated aspirin.

Studies on the role of tartrazine in aspirin-induced urticaria also showed inconsistent findings. When 40 aspirin-intolerant patients had a double-blind challenge with tartrazine, six out of 40 patients had a positive reaction [14]. In evaluating 10 patients with urticaria, Stevenson *et al.* [13] found only one patient reacted to challenge with a high dose of tartrazine (50 mg). However, that patient did not react to 650 mg of aspirin.

Gum

Several types of gum are used as emulsifiers. One of the commonly used is guar gum, which is extracted from the guar bean and used as stabilizer and emulsifier, particularly in ice creams, ketchups, salad dressings, yogurt, and baked goods.

When 16 workers with occupational asthma in environmental exposure to guar gum, flour, and psyllium were subjected to inhalation challenges to those agents after avoidance for an average of 5.7 years, a bronchospasm to any of those agents occurred in 11 workers [15]. In a case report [16] of a life-threatening hypersensitivity reaction following mucosal application of a local anesthetic containing guar gum, SPT was positive to guar gum and negative to multiple local anesthetics.

Monosodium glutamate

Monosodium glutamate (MSG) was originally obtained from seaweed and was later synthesized for wide distribution. It is a popular flavor enhancer added to many foods, especially Asian dishes. The average intake in a meal can be 3–5 g, with a widely varying daily intake per person that may reach 12 g in some countries [17]. Kwok [18] first described the clinical reactions to MSG in 1968 and coined the term 'Chinese restaurant syndrome'. A number of symptoms have been described, including numbness in the neck, which spreads to the arms and back, weakness, palpitation, headache, diaphoresis, flushing, and chest heaviness. Bronchospasm occurred only in patients with asthma. There are reports of asthma exacerbations due to MSG but no definite link was found in double-blind MSG challenges [19]. In a study [20] of 130 patients who claimed MSG-related symptoms, a positive challenge occurred in 53% of patients with up to 5 g of MSG and in 28% of patients to placebo. The symptoms were neither persistent nor serious. Furthermore, the reactions were inconsistent and not reproducible. No adverse effects were noticed when a dose of 3 g MSG was administered in 150 ml of beef bouillon at lunchtime to 73 healthy individuals either in an open or double-blind design [21]. In both the United States [22] and Europe [17], MSG is regarded as well tolerated.

Spices

Spices are derived from plants and used as flavoring agents. Because of the presence of capsaicin in hot spices, it may be difficult to differentiate intolerance from allergy, especially in children. A French study [23] showed that 2% of adults with food allergy have allergy to spices. Valuable information is available in a comprehensive review [24] on the allergenic potential of spices, including a list of spices not known to cause IgE-mediated reactions, which may be especially useful as alternative for spice-sensitive patients.

Aspartame

Aspartame (Equal; Merisant Company, Chicago, Illinois, USA, and NutraSweet; The NutraSweet Company, Chicago, Illinois, USA) is a commonly used artificial sweetener, 180 times sweeter than sucrose. It is often claimed as causing adverse reactions [25]. It has been reported as a cause of urticaria in some patients [26]. However, a well designed study [27] on 21 patients with alleged urticaria, angioedema, or both to ingestion of aspartame-containing products showed no difference between challenge testing with aspartame versus placebo.

Sulfiting agents

Sulfiting agents include sulphur dioxide and sulfites in the form of sodium salt (sodium sulfite, sodium bisulfite, or sodium metabisulfite) or potassium salt (potassium bisulfite or potassium metabisulfite). They are used to prevent browning of foods such as dried fruit, vegetables particularly salad bars and seafood. They also prolong shelf life, inhibit growth of microorganisms in the fermentation industry, and maintain the potency of certain medications. Common foods with high added sulfite content (>100 ppm) include dried fruits, grape juice, lemon and lime juice, molasses, pickled onions, and wines.

The prevalence of sulfite sensitivity was studied in a group of asthma patients; 83 patients were steroid dependent and 120 were nonsteroid dependent [28]. A single-blind oral challenge with potassium metabisulfite induced a reduction in forced expiratory volume in 1s (FEV₁) by greater than 20% in 19.3% of the steroid-dependent and in 4.2% of the nonsteroid-dependent group. When 12 of these sulfite reactors had a double-blind challenge, only three of seven steroid-dependent and one of five nonsteroid-dependent patients had a positive response. Accordingly, the overall prevalence was 3.9% (3/83) in the steroid-dependent and 0.8% in nonsteroid-dependent group.

The pathogenesis of sulfite sensitivity is not fully clear, and probably there is more than one mechanism [29]. The main effect seems to be primarily through inhalation of sulphur dioxide gas being generated during the digestion of sulfites causing bronchospasm. A second less

common mechanism is IgE-mediated type I hypersensitivity reactions. Yang *et al.* [30] reported that out of 53 patients with variety of symptoms related to either restaurant meals or alcoholic beverages, five patients had positive skin tests with sulfites. A third potential underlying mechanism is deficiency of the mitochondrial enzyme, sulfite oxidase, which oxidizes sulfite into sulphate, which is excreted as inactive substance. There are some reports of urticaria and angioedema with sulfites, but in 75 patients with chronic idiopathic urticaria, anaphylaxis, or both, blind challenges with 200 mg metabisulphite did not show a positive reaction [31]. In another series [32] of eight patients who claimed asthma exacerbation following wine ingestion, double-blind challenges did not induce a reduction in FEV₁ by more than 15% in any of the patients.

In the past, reactions to sulfites seemed to be increasing, which prompted a FDA regulation in 1986 of banning the use of sulfites in fresh fruits and vegetables intended to be sold raw to consumers, with the exception of potatoes. Shortly afterwards (January 1987), the FDA required that sulfites in finished foods must be declared on the label if present in quantities exceeding 10 ppm. Sulfiting agents are also used as an antioxidant in a number of pharmaceutical products, including epinephrine. However, the benefit of emergency administration of epinephrine in sulfite-sensitive patients far outweighs the remote possibility of a reaction [33,34].

Benzoates

Benzoates are food preservatives commonly used in alcoholic beverages, fruit juices, sparkling drinks, and pickles. They have been reported to cause bronchospasm in a few patients. In a double-blind oral challenge of 28 patients with persistent asthma, only one had a decrease of more than 20% in FEV₁ [35]. Double-blind oral challenge with monosodium benzoate in 226 patients with nonallergic rhinitis, positive subjective and objective symptoms developed in 8.8% and only positive subjective symptoms in another 8.4% [36]. These patients also reported symptom improvement within 1 month on a diet free of benzoates and other offending additives.

Food additives and behavioral problems

The effect of additives on children's behavior has been an area of interest to the public and to some degree to healthcare providers. Because of the nature of symptoms and time-related variability, well designed controlled studies are not easy to conduct on this subject. A well balanced review [37] indicates conflicting findings, but the evidence of a cause-and-effect relationship is generally weak.

Diagnosis

A detailed history taking is of utmost importance in suspecting additives as the underlying cause of a reaction. Physical examination may also reveal other causes of the patient's symptoms. Food additives should be suspected as the culprit if patients report a history of reactions to a number of unrelated foods or to a certain food when commercially prepared but not when prepared at home. A proposed diagnostic approach is as follows:

- (1) detailed medical history,
- (2) physical examination,
- (3) rule out allergy to common foods,
- (4) look for hidden foods the patient is allergic to,
- (5) possible skin prick testing or specific IgE to selected natural additives,
- (6) a trial of additive-free diet for a few weeks,
- (7) double-blind challenges with the suspected food additives.

In all patients, the reaction to main food components should be ruled out first. If the patient is known to have allergy to certain foods, suspect the presence of such food as a contaminant or incorporated under unfamiliar name. In this regard, complete labeling and careful reading of the ingredients might be helpful.

Skin testing or measuring specific IgE antibodies in the serum are of very limited value except in reactions to natural additives such as annatto [9], saffron [23], carmine [38], mannitol [39], and vegetable gums [40].

In most cases, the medical history and laboratory tests are unrevealing. An additive-free diet may be tried for a few weeks. Patients are advised to avoid all commercial and preprepared foods. In case of improvement, placebo-controlled, blind challenges with common additives can be performed using appropriate doses [6]. Initially, multiple additives can be combined in the challenge, and if there is a positive reaction, then individual additives need to be tested. The challenges should be appropriately designed to be safe and free of bias [41••].

Management

The major problem in dealing with reactions to additives is the identification of the offending agent(s). Once this is settled with certainty (blind challenge testing), the treatment is avoidance. To the best of our knowledge, there are no published reports on successful desensitization procedures.

Depending on the severity of anticipated reactions, patients should avoid commercially prepared foods as much as possible and to read labels. With the wide spread

Table 2 Example of a diet free of food additives

Meats	Beef, chicken, lamb, turkey, and veal (fresh or frozen)
Fish	Any (fresh or frozen)
Vegetables	Carrots, lettuce, mushrooms, and parsley
Cereal and grain	Rice
Fruits	Pears (canned, fresh, or nectar)
Cooking oil	Safflower without preservatives
Condiments	Honey, pepper, salt, and sugar
Beverages	Coffee, pear nectar, tea, and water
Optional	Butter, cottage cheese, eggs, matzo (plain), milk, preservative free bread, and spaghetti
Avoid	Apples, bananas, beer, breads not marked preservative-free, breakfast cereal, cakes, cheese, chocolate, fruit juices (except pear), grapes, instant foods, jams, licorice, margarine, mayonnaise, packaged meals, pickles, prepared salad dressings, prepared sauces, rhubarb, sweets, and wine

Modified from Wilson and Bahna [6].

of additive use, some patients may need to only eat food prepared at home from primary ingredients. Providing the patient with a list of foods that are unlikely to contain additives would be helpful (Table 2).

Despite all the precautions, accidental exposure is bound to happen. Hence, patients with a history of severe reactions should have self-injectable epinephrine and wear MedicAlert identification. The use of a long-acting antihistamine before an anticipated exposure might reduce the severity of a reaction. Leukotriene modifiers may be useful, particularly in patients sensitive to acetylsalicylic acid [42].

Conclusion

Despite the increased use of food additives, the prevalence of adverse reactions attributed to their use is very low in the general population and seems higher in atopic individuals. Food additives should be suspected as the culprit if patients report a history of reactions to a number of unrelated foods or to a certain food when commercially prepared but not when prepared at home. In all patients, reactions to the main food components should be ruled out first. Skin testing or measuring specific IgE antibodies to additives are of very limited value except for some natural additives. In most cases, the medical history and laboratory tests are unrevealing. An additive-free diet may be tried for a few weeks. If improvement occurs, placebo-controlled, blind challenges with common additives may identify the causative agent. Once the offending additives are confirmed, treatment is avoidance. To our knowledge, there are no published reports on successful desensitization procedures. Depending on the severity of anticipated reactions, patients should avoid commercially prepared foods as much as possible and to read labels. Because accidental exposure often occurs, patients with a history of severe reactions should

have self-injectable epinephrine and wear MedicAlert identification.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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