

REACTIONS TO FOOD ADDITIVES

C Royal | MBChB (UCT), FCPaed (SA)

M Levin | MBChB, FCPaed (SA), Dip Allergy (SA), MMed (Paed), PhD, EAACI Allergy Exam (UEMS), FAAAAI, FAAAAI

Paediatric Allergology, Red Cross War Memorial Children's Hospital

Email | candiceroyal@gmail.com

ABSTRACT

Food additives are natural or synthetic substances that are added to food to enhance their preservation, palatability and appearance or to alter and stabilise form. Their ubiquitous use and ability to cause a wide spectrum of clinical reactions in sensitive individuals means that they are an important consideration when managing reactions to food. The case below describes a child with a severe preservative reaction who presented to the Allergy Division at the Red Cross War Memorial Children's Hospital. This is followed by an overview on reactions to food additives with an emphasis on some of the common additives and their clinical relevance.

CASE

A 12-year-old female was referred to the allergy clinic at the Red Cross War Memorial Children's Hospital following two severe allergic reactions on the background of presumed chronic spontaneous urticaria. She first developed urticaria and angioedema of her face and lips two hours after ingesting ten pieces of pickled watermelon at a supermarket. This episode was associated with an acute onset of coughing and difficulty in breathing. Her symptoms resolved within a few hours; however, within the same month, she experienced similar symptoms following a meal of salad and tinned tuna with mayonnaise at her school cafeteria. On this occasion, she also had a hoarse voice, difficulty in breathing and reported the sensation of 'tightness' in her chest. Her symptoms resolved prior to seeking medical attention.

Two weeks after this second incident, she presented to the outpatient department, describing two further episodes of urticaria with no systemic symptoms. She was commenced on daily cetirizine with a presumptive diagnosis of chronic spontaneous urticaria (normal physical examination, normal full blood count and differential count, normal erythrocyte sedimentation rate) and was referred to the allergy clinic. At this visit she continued to report frequent episodes of urticaria and angioedema but had had no further severe reactions. A detailed history was taken which revealed that these reactions followed closely after the intake of certain fruit juices, cooldrinks and condiments. She had previously eaten fresh watermelon and fish (including tuna) with no reaction. Her regular diet had no specific exclusions and contained both dairy products and eggs.

Our presumptive diagnosis was a severe preservative hypersensitivity rather than a reaction to the native foods.

To confirm this, we undertook the following investigations: a cellular antigen stimulation test (CAST) ELISA (enzyme-linked immunosorbent assay) for preservatives and specific IgE measurements for watermelon and tuna. A skin-prick test (SPT) could not be performed as the patient was on antihistamines. She was advised to avoid preservatives and consulted the clinic's dietitian for help with dietary modification.

Her results were supportive of a preservative hypersensitivity:

1. Specific IgE to watermelon and tuna both <0.1 kU/l
2. CAST (Table I)

TABLE I

Food additive	Patient's result	Technical cut-off
Sodium benzoate	23 pg/ml	90 pg/ml
Food colourant mix 1	17 pg/ml	160 pg/ml
Tartrazine	0 pg/ml	120 pg/ml
Sodium nitrate	0 pg/ml	60 pg/ml
Potassium metabisulphite	0 pg/ml	40 pg/ml
Quinolone yellow	14 pg/ml	200 pg/ml

At her review appointment two months later she had successfully followed a preservative-free diet and had had no further reactions, including no further urticaria. The possibility of performing an in-hospital challenge to sodium benzoate was discussed with the family; however, the patient was unwilling and the challenge was deferred. In view of the presence of systemic symptoms during the patient's reactions and the potential for accidental exposure she was provided with an action plan and an adrenalin auto-injector. The patient and her family received extensive counselling regarding the avoidance of preservatives, managing hypersensitivity reactions and

use of the adrenalin auto-injector. An application for a Medic-Alert disc reflecting the potential for severe reaction to sodium benzoate has been made.

FOOD ADDITIVES

Food additives are substances added to food at any stage of its production, processing, treatment, packaging, transportation or storage.¹ They can be natural or synthetic.² There is much public interest in the potential of food additives to cause adverse reactions, but well-designed and conclusive trials for many relevant additives are lacking in the current literature.

Food hypersensitivity is an adverse reaction to a food at a dose which is usually tolerated by a normal individual. Food intolerance is an adverse reaction to a food which does not involve the immune system. It is caused by toxic, pharmacological, metabolic or idiosyncratic reactions to the food or to chemical substances in the food. A food allergy reaction comprises a hypersensitivity reaction that is mediated via the immune system. Such reactions may be IgE-mediated, non-IgE-mediated or mixed.

The true prevalence of food-additive hypersensitivity is difficult to determine due to the lack of reliable diagnostic tests. The current literature estimates the prevalence to be between 0.01% and 2%.^{2,3} This figure may be up to 7% in children with allergies.⁴ Food intolerances to naturally occurring food chemicals may be more common than those to synthetic substances.⁵

At present, the mechanism involved in many of the reactions to food additives is unknown. The clinical manifestations of a food-additive hypersensitivity are varied and may affect multiple organ systems. The range of possible presentations includes worsening or provocation of allergic diseases including asthma, atopic dermatitis, allergic rhinitis and urticaria as well as hypersensitivity reactions, both cutaneous and systemic. Hypersensitivity to preservatives, including benzoates, is usually due to a non-immune-mediated food intolerance. While 'type 1'-like symptoms may be produced, true food allergy occurs uncommonly and these symptoms are thought to be produced via other pathways. The severity of the reactions may range from mild to anaphylactic, as illustrated by the case described above.⁶ A dose-dependent increase in the severity of the reaction is well described.

Natural food additives are more commonly implicated in anaphylactic reactions than synthetic additives, and increasing consumer preference for only 'natural' ingredients has caused a rise in IgE-mediated reactions to these substances. Among those implicated are annatto, carmine, guar gum and psyllium.⁷ Synthetic food additives that have been reported to cause anaphylaxis include sulphites and sodium benzoates.^{8,9}

Identifying a reaction to a food additive can be complex and the lack of definitive tests brings comprehensive history-taking to the forefront. Suggestive situations include: adverse reactions to multiple unrelated foods, a temporal association of the reaction with food ingestion and in the circumstance where a food is tolerated when prepared at home but not when commercially prepared.^{1,10} A thorough physical examination is required to exclude an underlying medical condition that may be responsible for the symptoms, such as thyroid disease, autoimmune disorders and underlying malignancies. Skin prick testing or specific IgE testing is useful in excluding IgE-mediated allergy to the main food components. Patch testing is used in evaluating delayed reactions to food or in eliciting the inciting agent in contact dermatitis, but it has not been validated for the diagnosis of food additive hypersensitivity.

A CAST ELISA has some use in investigating reactions to food additives; however, if it is negative a clinical reaction cannot be completely excluded. Furthermore, reference ranges given for a 'positive' test to various allergens are based on +3SD above the mean of net stimulation from stimulated samples from normal blood donors.¹¹ The ranges therefore exist as a guideline only and results should be interpreted within the clinical context. As in IgE-mediated food allergy, the presence of a raised result alone is not sufficient for a diagnosis of food allergy. Conversely, a raised result along with a highly suggestive history may be sufficient to diagnose and manage as a food allergy without recourse to a food challenge.

A CAST ELISA is an *in vitro* test that assesses the production of leukotrienes by the patient's basophils following stimulation by the allergen under investigation. This may be via IgE-dependent or non-IgE-dependent mechanisms. Other laboratories may use a Flow CAST (Basophil Activation Test), which uses flow cytometry to identify basophils activated *in vitro* by the relevant allergen via expression of the CD63 molecule.

Elimination diets may be useful to strengthen a diagnosis of a food-additive hypersensitivity. An oral-food challenge with the additive in question is confirmatory.¹²

Treatment comprises avoidance once the offending agent is identified. Patients require education regarding the common foods in which the additive may be found and the nomenclature that may be used in food labelling. In those in whom severe reactions are anticipated, a chronic and acute care plan should be devised, a Medic-Alert disc should be provided and an adrenalin auto-injector supplied along with appropriate education and training in its use.

PRESERVATIVES

Sulphites

Sulphite preservatives are effective, inexpensive and versatile and are therefore widely used in processed

food, beverages, cosmetics and medication.¹³ They may be added to fresh fruits or vegetables in restaurants or supermarkets to preserve colour, although in many countries this has been outlawed. The various agents are chemically equivalent and designated by E numbers 220–228. Their preservative function in food is mediated via conversion to sulphur dioxide.

The adverse effects to sulphites in sensitive individuals range from limited cutaneous to life-threatening anaphylactic reactions and this may be dependent on the degree of individual sensitivity, the dose of exposure and whether the sulphite is in a bound or an unbound form. Sulphites are able to provoke bronchoconstriction in 3–10% of asthmatics via oral ingestion or occasionally from the inhalation of aerosolised sulphites in cold drinks. This figure may be even higher in steroid-dependent patients and in children.¹³ Postulated mechanisms include a reduced level of sulphite-oxidase in asthmatics or sulphite stimulation of the parasympathetic system with resultant bronchospasm. The effects on various prostaglandins and leukotrienes have been demonstrated and it is likely that multiple mechanisms are involved.¹⁴ Sulphite-sensitive asthma can be confirmed by demonstrating a reduction in the forced expiratory volume in one second (FEV₁) following a sulphur dioxide inhalation challenge.¹⁵

Benzoates

Benzoates such as benzoic acid and sodium benzoate have been added to foods since the 1900s and, currently, are among the most widely used food additives. Benzoates are used as preservatives in foods and beverages with an acidic pH (see Table II). They also occur naturally in prunes, cinnamon, cloves, tea, anise and many berries.

TABLE II

Food additive	Common sources
Sulphites	Beer and wine, fruit juices, cordials, jams, gravies and sauces, gelatine, coconut, restaurant salads, fruit salads.
Sodium benzoate	Salad dressings, carbonated drinks, jams, pickles, fruit juices and condiments including mayonnaise, cheeses and frozen dairy products.
Monosodium glutamate	Dried soup mixes, potato chips, crackers, diet foods and in the restaurant industry to flavour savoury dishes.

Intolerance to benzoates has been implicated in some cases of allergic and non-allergic rhinitis¹⁶ and asthma; however, large well-designed trials have not conclusively linked persistent asthma and benzoate intolerance.¹⁷ A synergistic role in provoking bronchoconstriction in asthmatics has been suggested when aspirin is used in combination with benzoates.¹⁸

Reactivity to benzoates in patients with chronic urticaria (CU) is thought to be rare.¹⁹ Natural sources of benzoates have

not been implicated in toxic or hypersensitivity reactions but may play a role in CU and orofacial granulomatosis. Benzoate elimination diets used in the treatment of these conditions usually suggest the avoidance of naturally occurring benzoate.²⁰

Melkersson-Rosenthal Syndrome or Oropharyngeal granulomatosis is a rare disorder that is characterised by lip granulomas, facial paralysis and a fissured tongue. In individuals with the condition 60 per cent are atopic and food additives, particularly benzoates, have been identified as causative factors.²¹

FLAVOURANTS

Monosodium glutamate (MSG)

MSG is added to enhance the flavour of predominantly savoury products. It is also widely used in the restaurant industry, especially in Asian food.

'Chinese restaurant syndrome' refers to a rare symptom complex of pain and numbness spreading from the neck down the arms, headache, flushing, abdominal pain and palpitations, that has been reported to follow ingestion of a high quantity of MSG. Symptoms occur within 30 minutes of the meal and persist for up to two hours with spontaneous resolution.²²

The literature regarding the provocation of bronchoconstriction in asthmatics by MSG remains conflicting. Other reported reactions include a worsening of atopic dermatitis,²³ exacerbating or inducing urticaria and angioedema,²⁴ precipitating migraine headaches²⁵ and mood disturbances.²⁶ Further data is required to prove causality conclusively in these reactions.

COLOURANTS

Colourants may be natural or synthetic. Naturally occurring dyes such as annatto, carmine and saffron have been implicated in IgE-mediated reactions, including anaphylaxis. The implication of food dyes in adverse reactions to food is based on uncommon reactions seen in sensitive individuals.⁷ It is highly controversial whether food dyes play a role in hyperkinesia and behavioural problems in children.²⁷ Tartrazine is an azo dye that is widely used in food and pharmaceuticals. It has been proposed as a trigger for urticaria and bronchoconstriction in asthma. A Cochrane review concluded that tartrazine avoidance is unlikely to be beneficial in asthma control, except in those with proven sensitivity.²⁸

EMULSIFIERS AND STABILISERS

The function of emulsifiers and stabilisers is to facilitate the mixing together of ingredients that normally would not mix, namely fat and water. They are seldom implicated in food intolerances but in the case of lecithin, may serve as a 'hidden' allergen precipitating IgE-mediated food allergy in egg- or soya-allergic individuals.⁶

CONCLUSION

Food additives are widely used in the manufacture and processing of a large range of foods. Hypersensitivity reactions to these agents are thought to be uncommon, but prevalence may be greater in atopic individuals, especially children. Reactions are variable, even in individuals, and may include anaphylaxis. In view of the lack of confirmatory tests, diagnosis relies on meticulous history-taking and an awareness of 'hidden ingredients'. Management involves

careful avoidance through label reading, but due to the high risk of accidental exposure, individuals with severe reactions should be provided with education and access to an adrenalin auto-injector.

DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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