

Food additives intolerance: A possible cause of perennial rhinitis

To the Editor:

The medical literature overflows with papers claiming that food additives are responsible for an array of conditions ranging from urticaria to behavioral disturbances.^{1,2} Nevertheless, the relevance of these substances in allergic diseases is still unclear, inasmuch as most published studies have been either anecdotal or heavily biased. Clearly, only well-designed studies (double-blind and placebo-controlled, with multiple and randomized placebos) can help to clearly establish the role played by food additives in allergic disorders.

A case of perennial rhinitis caused by sodium benzoate, showing that chronic allergylike symptoms of the upper respiratory tract might be secondary to food intolerance, was recently observed in this allergy center.³ The present study describes 3 further cases of additive-induced rhinitis, indicating that this condition is probably not uncommon.

All patients with perennial rhinitis seen at this allergy center from January 1, 2001, through December 31, 2001, were considered eligible for the study. In view of our previous observations,³ only those fulfilling all of the following criteria were included:

1. Long-lasting (>6 months) rhinitis with "allergic features," including watery rhinorrhea, itching of the nasal mucosa, and episodes of sneezing paroxysm
2. Diagnosis of "allergic rhinitis" in the absence of both structural deformities and nasal polyps on ear, nose, and throat investigation
3. Normal computed tomography scan or plain radiographs
4. Negative skin prick test results with the common airborne allergens, including pollen (grass, mugwort, ragweed, olive, birch, cypress, pellitory, and plantain), mites, molds (*Alternaria*, *Aspergillus*, *Cladosporium*), and dander of several animals
5. Total disappearance of nasal symptoms a few days after the start of an elimination diet (free of food additives) and persistent absence of rhinitis for 1 month while on restricted diet regimen
6. Relapse of nasal symptoms within a period of days after the start of an open challenge test (unrestricted diet) and their persistence during 3 weeks of unrestricted diet
7. New total and persistent disappearance of rhinitis some days after the resumption of the elimination diet.

Fifty-four patients fulfilled the first 4 of these criteria, but only 3 (6%) of these (2 men and 1 woman; age, 45-58 years; disease duration, 6-48 months) fulfilled the last 3 criteria as well and were included in the present study. In all 3 cases antihistamines were able to induce partial relief.

Each of the 3 subjects underwent double-blind, placebo-controlled peroral challenges with food additives. Substances and doses given are shown in Table I. Patients continued to follow the additive-free diet regimen throughout the study period and were not allowed to use antihistamines or corticosteroids. Active substances and multiple placebos (talc) were given in opaque capsules, 1 week apart and in a randomized sequence. Both active substances and placebos were given as single doses. Each patient was challenged with all active substances listed in Table I and with 3 placebos, and each was kept under control for 2 hours at the allergy center after each provocative dose. All patients gave an informed written consent before the start of the challenge procedure. Only the appearance of acute rhinitis mimicking the original clinical features was considered to be a positive response.

All 3 patients reacted after the administration of a single active substance only (monosodium glutamate [MSG] in 2 cases, sodium benzoate in 1 case). In all cases the offending additive induced severe rhinitis from 4 to 6 hours after the administration; symptoms

TABLE I. Food additives used in challenge tests

Additive	Dose (mg)
Sodium metabisulfite	25
Sodium benzoate	200
Monosodium glutamate	100
Sodium nitrate	10
Tartrazine	10
Erythrosine	10
Sorbic acid	100
Butylated hydroxyanisole	10
Talc (placebo)	100

lasted for 2 days in the 2 MSG-intolerant subjects and for 1 week in the sodium benzoate-intolerant subject. One of the MSG-intolerant subjects agreed to undergo a second confirmatory series of double-blind, placebo-controlled challenges, including MSG 100 mg and 2 placebos in a randomized sequence. Again, only the active substance induced rhinitis, which lasted for 48 hours.

This study provides further evidence that food additives intolerance might present clinically as chronic allergylike rhinitis. In a previous study, the culprit was sodium benzoate,³ and we recently reported a patient with multiple-additives intolerance who experienced rhinitis after the ingestion of both sodium metabisulfite and the antioxidant butylated hydroxyanisole.⁴ As in those studies, bias in the present investigation should have been minimized by the diagnostic procedure used (double-blind and placebo-controlled, with multiple placebos) and by the fact that a second series of confirmatory challenges was carried out in 1 patient. This is probably the first study to show that perennial rhinitis might be secondary to MSG intolerance.

The pathogenesis of these adverse reactions remains unclear. The effect of the offending additives was rather long-lasting (particularly in the case of the benzoate-intolerant subject), given that in subjects with IgE-mediated, food-induced rhinitis symptoms rarely last more than a few hours, even without treatment.^{5,6} The fact that symptoms were partially controlled by antihistamines suggests a mechanism based (at least in part) on direct histamine release from mast cells, but it also suggests that histamine might be only one of several mediators of inflammation induced. The reasons that offending food additives appear to induce inflammation only at the level of a specific target organ (the nose) and not at different sites (eg, lungs or skin) remain to be elucidated.

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Are all IGIVs the same?

To the Editor:

As informed physicians who regularly infuse immune globulin intravenous (human) (IGIV) in patients with different diseases, we are concerned about a "Dear Healthcare Provider" letter that was recently issued by Baxter Healthcare Corporation (March 26, 2002). The letter advises caution in terms of the risks of thrombotic events after IGIV infusions and, by association, risks attributed to the rate of infusion and the (percent) concentration of the solution.

Such letters, without ample review of the findings with all products and the full spectrum of patients receiving IGIV, run the risk of jeopardizing many IGIV infusion programs. Although caution needs to be exercised with regard to all aspects of an IGIV infusion, we want to emphasize that not all preparations are the same and that certain properties of a product, such as osmolality and the use of sugar stabilizers, are more likely than others to impact the risk of adverse events.

These issues are very pertinent in their reference to the report by Grillo et al.¹ The role of osmolality and sugar content have already been noted in the cautionary report of the association of renal failure and IGIV infusions.² Increased osmolality is common to lyophilized preparations that contain sugars as a stabilizer.

There is ample evidence for the safety of IGIV preparations of 10% concentration and rates of infusion recommended in the

respective package inserts that are higher than the maximum rate of 4 mL/kg body weight per hour suggested in the letter. The use of higher concentrations or more rapid rates of infusion are not choices of convenience, as alluded to in the letter, but are integral components of infusion programs that value safety, efficacy, and compliance while avoiding lengthy and intolerable infusion times and reducing fluid load.

Continued pharmacovigilance is essential, as is appropriate identification of where the problems lie. We expect all manufacturers of IGIV to examine and report on their safety data. Solutions that are at least iso-osmolar or sugar-free might be important choices, especially in patients receiving higher IGIV doses, as is the case in the treatment of many autoimmune, allergic, and neurologic diseases today.

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