

Original Article

Prevalence of Sensitivity to Food and Drug Additives in Patients With Chronic Idiopathic Urticaria

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What is already known about this topic? Food and drug additives have been implicated as the source for exacerbation of chronic idiopathic urticaria.

What does this article add to our knowledge? This study demonstrated that food and drug additives appear to be a rare cause of exacerbation of chronic idiopathic urticaria.

How does this study impact current management guidelines? Avoidance of food and drug additives in patients with chronic idiopathic urticaria is not recommended.

BACKGROUND: Chronic idiopathic urticaria (CIU) is defined as the presence of urticaria most days of the week for a period of 6 weeks or longer. There have been reports of food additive sensitivity in CIU previously, but the prevalence has not been precisely determined.

OBJECTIVE: To determine the prevalence of reactions to food and drug additives in patients with CIU.

METHODS: We challenged 100 patients in our allergy/immunology division with CIU to the 11 additives most commonly associated with reactions: tartrazine (FD&C Yellow 5), potassium metabisulfite, monosodium glutamate, aspartame, sodium benzoate, methyl paraben, butylated hydroxy anisole, butylated hydroxy toluene, FD&C Yellow 6, sodium nitrate, sodium nitrite. All of the patients had a history of CIU for longer than 6 weeks, and 43 reported possible history of food or drug additive sensitivity. Single-blind challenges to all of the additives were performed in the clinic and skin scores were recorded. Subjects with positive challenge tests underwent double-blind placebo controlled challenges.

RESULTS: Of 100 subjects, only 2 had a positive urticarial response on single-blind challenge. Neither of these patients had a positive urticarial response on double-blind placebo-controlled challenge. There were no gastrointestinal, respiratory, or other symptom, and no patients reported late reactions.

CONCLUSION: We were able to conclude, with 95% confidence intervals that sensitivity to any of the 11 food and drug additives occurs in fewer than 1% of patients with CIU. Food and drug additives appear to be a rare cause of CIU, and avoidance is not recommended. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;■:■-■)

Key words: Food additives; Drug additives; Chronic idiopathic urticaria

Food additives are used throughout the food industry for an array of purposes, including flavoring, coloring, preservation, and emulsification. Some of these agents have been considered as sources for adverse reactions, such as asthma, urticaria and/or angioedema, and anaphylaxis.¹ Chronic idiopathic urticaria (CIU) is defined as the presence of urticaria (hives) most days of the week for a period of 6 weeks or longer. Patients often try to associate the presence of their symptoms with specific foods or food additives; however, clinically relevant allergies to foods or additives are uncommon in these patients.² In the case of urticaria, it is often difficult to determine whether a food or a drug additive was the source of exacerbation given that this condition tends to wax and wane naturally throughout any given day and also over time.³

Challenge studies can be used to confirm the association of an adverse reaction with a particular substance and may be helpful for a clinician providing recommendations regarding avoidance. Consideration must be made regarding the time interval between the last dose of antihistamine and the administration of a placebo in the challenge sequence. If antihistamines are held before challenge, then a coincidental increase in skin symptoms may occur, although unrelated to challenge. Therefore, it may be advantageous to continue use of antihistamines during challenge.³

Oral challenge studies also can be used to determine the prevalence of sensitivity for foods or food additives in a subject population. Results of prior studies have suggested a prevalence of between 1% and 68%. However, these studies were not rigorously controlled nor used quantifiable objective parameters

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*Abbreviations used**CIU- Chronic idiopathic urticaria**FD&C- Federal Food Drug and Cosmetic Act**MSG- Monosodium glutamate*

to determine a positive reaction. In the case of tartrazine (Federal Food Drug and Cosmetic Act [FD&C] Yellow 5), many of the previous studies showed positive reactions; however, it is unclear if this was due to breakthrough urticaria from withholding antihistamines or a false-positive reaction due to the order effect of administering placebo first.³

A case report of sulfite-induced urticaria was confirmed by a double-blind placebo-controlled challenge.⁴ However, Simon⁵ was unable to demonstrate a positive reaction to encapsulated metabisulfite in 75 patients with chronic urticaria. Monosodium glutamate (MSG), which has been used as a flavor enhancer both occurring naturally and added to many foods, does not appear to be a significant cause for exacerbation of chronic urticaria. In a study of 65 patients with CIU, 2 patients had a positive response on single-blind challenge to MSG, but neither responded in a double-blind, placebo-controlled challenge.⁶ Aspartame was previously studied in a randomized double-blind, placebo-controlled study and was found to be no more likely than placebo to elicit urticaria.⁷

Sodium benzoate, methyl paraben, butylated hydroxyanisole, butylated hydroxytoluene, nitrates, and nitrites were associated with prior reports of adverse reactions; however, the majority of studies had the same design flaws as prior tartrazine studies in which antihistamines were withheld before and during drug challenges, or no information was provided on antihistamine status. Sodium benzoate, which is commonly used for antimicrobial properties in foods, and methyl paraben, which can be used as a food, pharmaceutical, and cosmetic preservative, have also been implicated as provokers of chronic urticaria. Warin and Smith⁸ evaluated 111 patients with chronic urticaria in which antihistamines were continued and found the prevalence of reactions to be 5% for parabens and 11% for sodium benzoate. Sodium nitrate and sodium nitrite, which are used as curing agents in meat production, were not found to cause an urticaria exacerbation in 226 patients in a study by Volonakis et al⁹ in which patients were challenged with 100 mg of nitrate-nitrite. Moneret-Vautrin et al¹⁰ found 4 patients in whom sodium nitrite caused provocation of chronic urticaria in a double-blind placebo-controlled challenge.¹⁰ However, in the study by Warin and Smith,⁸ no definition was given for a positive reaction, and, in the Volonakis et al⁹ report a reaction was considered positive if the patient developed definite urticaria or angioedema within 24 hours of challenge. Given the prior design flaws in terms of withholding of antihistamines, timing of placebo, and using semiquantitative criteria for a positive reaction, our primary objective was to determine a more accurate assessment of prevalence of reactions to food and drug additives in patients with CIU.

METHODS

Study design

Challenges, by using 11 food additives, were prospectively performed over a 10-year period in patients with CIU in our allergy/immunology division.

TABLE I. Skin scores

Urticarial lesions	Points
None	0
Isolated	1
<25% of area	2
<50% of area	3
≥50% of area	4

Patient selection

All patients with CIU in our allergy/immunology division were offered additive challenge. A total of 100 patients with CIU (36 male patients and 64 female patients), ages ranging from 14 to 67 years, were challenged. CIU was defined as urticaria for more than 6 weeks without discernible etiology. Each patient studied had active urticaria at the time of challenge. For those with persistent urticaria despite antihistamines at the time of enrollment, no changes were made in medications. For patients whose hives were completely suppressed by their current antihistamine dose, their dose was reduced until hives returned at a tolerable level. This was defined as the minimum effective dose, which was individualized for each patient. None of the patients were on immunosuppressant therapy. Patients were not excluded if they reported a possible history of food or drug additive allergy, although only 43 reported this. Patients were excluded if they had physical urticaria or cutaneous vasculitis. Written, informed consent for additive challenge was received from all research subjects in compliance with Scripps Institutional Review Board.

Skin scores

The scoring system based on the “Rule of Nines” was used to determine positive challenge.¹¹ The body is divided into areas of 9%, which are then scored on a scale from 0 to 4 (Table I). Body areas included were head/neck, right arm, left arm, chest/abdomen, back, right thigh, left thigh, right leg/foot, left leg/foot. When the chest/abdomen and back areas were recorded, scores were multiplied by 2. Zero points were given for no urticarial lesions, 1 point for isolated lesions, 2 points for <25% of the area, 3 points for <50% of area, and 4 points for >50% of the area. The maximum possible score was 44. A positive response was defined as either an absolute increase in the total skin score of at least 9 points or an increase of more than 30% from the baseline score, in similar fashion to determining the degree of involvement in a burn patient. Skin scores were determined by either an allergy division registered nurse or a clinical fellow.

Food additives

Eleven food additives were selected that have been associated most commonly with reactions. These were obtained from the University Compounding Pharmacy (San Diego, Calif). The additives tested were tartrazine (FD&C Yellow 5), potassium metabisulfite, MSG, aspartame, sodium benzoate, methyl paraben, butylated hydroxy anisole, butylated hydroxy toluene, FD&C Yellow 6, sodium nitrate, and sodium nitrite. Doses of food additives were determined based on human exposure studies in the National Library of Medicine Database, which listed the maximum amount of food additive that can be consumed in a 24-hour period in one's diet. Food additives and doses in milligrams are listed in Table II.

TABLE II. Additives tested and doses

	Doses (mg)
FD&C yellow 5	50
FD&C yellow 6	50
K+ metabisulfite	100
MSG	2500
Aspartame	150
Sodium benzoate	100
Methyl paraben	100
Butylated hydroxyanisole	250
Butylated hydroxytoluene	250
Sodium nitrate	50
Sodium nitrite	50

Single-blind challenges

Single-blind challenges were performed as screening challenges in the clinic under the supervision of a physician. Baseline assessment of urticaria was recorded for 3 consecutive days before the day of challenge. The patients were simultaneously challenged to all 11 additives given in 15 opaque capsules. Skin symptoms were recorded hourly after administration of food additive capsules for 4 hours. The patients were instructed to continue to check skin at 6 and 8 hours after ingestion at home and to call the physician the following day if additional skin symptoms arose.

Double-blind placebo-controlled challenges

The patients with positive single-blind challenges were admitted to the clinical research center for double-blind placebo-controlled challenges. A minimum of 2 weeks had elapsed between single-blind challenge and double-blind placebo-controlled challenges. Double-blind challenges were performed with multiple placebos with sucrose and 1 food additive, 2 hours apart, on each of 11 separate days.

Statistical analysis

In this high-risk population, the exact confidence intervals for the binomial response probability were calculated for 100 patients.

RESULTS

Baseline characteristics

The allergy/immunology division of Scripps Clinic challenged 100 patients with CIU who met the inclusion and exclusion criteria. The patient demographics are described in Table III. Patient ages ranged from 14 to 67 years. The majority of these patients were girls and women (64%). Forty-three patients reported a history of prior adverse food additive reactions. The duration of hives in these patients was 3-52 months, with a mean of 9 months.

Single-blind challenge outcomes

Although there was no apparent clinical reaction to the patient or the observer with any of the 100 patients challenged, 2 had a positive urticarial response as evidence by positive skin score. These 2 patients did not have any clinically distinguishing factors. One patient reported a history of adverse food additive reaction, and one did not. Both of these patients then waited at

TABLE III. Patient characteristics: Demographics

	No. of patients
Total	100
Sex	
Female	64 (64%)
Male	36 (36%)
History of adverse food additive reactions	43
Sulfite	5
FD&C Yellow 3	14
Sulfite + FD&C Yellow 5	8
MSG	10
FD&C red 40	2
FD&C blue 1	1
Preservatives and/or chemicals	15

least 2 weeks before double-blind placebo-controlled challenge. None of the patients reported a late reaction.

Double-blind placebo-controlled challenge outcomes

Two patients were challenged with 11 individual food additives in our clinical research center. Neither of these subjects had a positive urticarial response. Thus, the prevalence of food additive sensitivity in CIU patients is <1%, 95% probability (CI, 0, 0.36).

DISCUSSION

The primary result of this study is that reactivity to any of the commonly implicated food additives in patients with CIU occurs only rarely. Even in this "high-risk" population in which 43 of our subjects had previously reported a history of reaction to food or drug additives, analysis of our data suggests that prevalence is less than 1%. Prior reports had implicated tartrazine, benzoates, and parabens to occasionally aggravate chronic urticaria. Also aspartame, butylated hydroxy anisole, and butylated hydroxy toluene have previously been shown to be the cause of isolated cases of CIU. MSG has been described in prior case reports as causing urticaria and angioedema.¹² These 7 food additives as well as 4 others were all included in our challenge.

Previous studies have reported a prevalence of reaction to food and drug additives that ranged from 2%-68%. A double-blind placebo-controlled study by Hannuksela and Lahti¹³ found 1 patient, with sensitivity to 200 mg of benzoic acid of 44 patients with chronic urticaria. Many prior studies have been performed after withholding antihistamines. For example, in a single-blind study by Juhlin,¹⁴ 31% of patients tested were found to have one or more positive reactions. However, these patients' antihistamines were withheld, which may have led to false-positive results. Also, 20% of patients in the study by Juhlin¹⁴ were noted to have exercise-induced urticaria and, therefore, not idiopathic urticaria. Another concern is the continuation of antihistamines through other studies, which may have led to false-negative results. To circumvent both of these issues in this study, antihistamines were reduced to their minimum effective dose.

In several studies, there was no standardized scoring system used to determine a positive response, which is of particular concern in single-blinded studies. For example, in a study by Genton et al,¹⁵ a test was considered positive if angioneurotic edema and/or urticaria were "noticed by a physician during the

18-hour period after the test.” As a result, 15 of 17 patients with urticaria were found to have positive responses after single-blind challenge with 5 additives and 2 drugs.¹⁵ This also was seen in a study by Supramaniam and Warner,¹⁶ in which 43 children with CIU and/or angioedema were challenged with 10 individual food additives, and 24 were found to react to at least 1 additive. In this study, the primary criterion for a positive reaction “was the appearance of urticaria or angioedema.”¹⁶

There have also been reports of an order effect of challenge in which a patient initially receives placebo and experiences no reaction, however, experiences a reaction on subsequent challenge regardless of challenge substance.³ This appeared to be a confounding factor in many prior additive studies; therefore, placebo administration was randomized in our double-blind studies.¹

If a clinician suspects that a patient with CIU has a food additive sensitivity, then single-blind challenge with a placebo control should be performed initially. If there is any objective evidence of reaction, then double-blind placebo-controlled challenge should be performed with multiple placebos to confirm the sensitivity. However, if there is no response to single-blind challenge, then it is unlikely that additives are the culprit.³ A presumptive diagnosis of adverse reaction to the additive can be made if the patient continues to have objective findings during double-blind placebo-controlled challenge and if their CIU improves after dietary avoidance. The patient’s medications and state of activity of his or her urticaria at the time of challenge should also be taken into account, and challenge may need to be repeated to ensure that results are reproducible.

Additive-free diets do not appear to be helpful for patients as a means of diagnosis. Patients often initially have improvement of symptoms but gradual reintroduction of food additives may not lead to resumption of symptoms due to the natural course of CIU. Patients also may have waxing and waning of symptoms after resumption of a full diet and, therefore, are unable to clarify what was the offending agent.² A recent study found that, in patients with CIU, although a significant change in urticarial symptom score was noted after initiation of a food additive-free diet, no patients experienced remission of their urticaria.¹⁷ In

conclusion, sensitivity to food additives appears to be rare in patients with CIU, and avoidance is not recommended.

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