

Suspected tartrazine-induced acute urticaria/angioedema is only rarely reproducible by oral rechallenge

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Summary

Background Tartrazine has been frequently linked to several diseases. However, a cause-and-effect role for tartrazine in these illnesses, especially in urticaria, has not always been established.

Objective The aim of this study is to determine the incidence of intolerance to tartrazine among subjects who experienced an acute episode of urticaria/angioedema following the ingestion of a meal or a product containing this substance.

Methods This was a retrospective study based on analysis of data of patients reported to have experienced episodes of urticaria and/or angioedema after ingesting meals or products containing tartrazine. At the first visit to the outpatients clinic, a careful anamnesis had been taken. Patients had then been submitted to the following diagnostic tests: IgE tests to common inhalant allergens and food allergens and a double-blind placebo-controlled challenge with tartrazine.

Results A total of 102 subjects were enrolled in the study: 19 (18.6%) showed at least one relevant positive reaction to an IgE test for food allergy. Only one subject (1%) had reactions after ingestion of 5 mg of tartrazine, given on day 5. She did not have adverse reactions to placebo.

Conclusion This study shows that the percentage of acute urticaria and/or angioedema induced by tartrazine is very low (1%). In view of our results, we suggest that all physicians with patients who have suffered adverse reactions that could be attributed to tartrazine should also carefully evaluate other possible causes.

Keywords double-blind placebo-controlled challenge, tartrazine, urticaria/angioedema

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Introduction

Tartrazine is used worldwide as a colourant. As reported by the European Parliament and Council Directive 94/36/EC of 30 June 1994, tartrazine can be used singly or in combination with other food colouring and, if required other food additives, in several foods such as non-alcoholic flavoured drinks, candied fruits and vegetables, confectionery, decorations and coatings, fine bakery products (e.g. biscuits, cakes and wafers), edible ices, flavoured processed cheese, desserts including flavoured milk products, sauces, mustard, snacks and food supplements/dietary integrators.

In 1959, Lockey [1] was the first to describe a case of urticaria due to tartrazine. Since then, reports have been published of many adverse reactions linked to this colourant whose pathogenetic mechanisms remain unknown. To date, the prevalence of tartrazine sensitivity in the general population cannot be determined, although in a study by Young et al. [2] it is estimated to be 0–0.12%.

The aim of this study is to determine the incidence of intolerance to tartrazine among subjects who experienced an

acute episode of urticaria/angioedema following the ingestion of a meal or a product containing this substance.

Materials and methods

Subject characteristics

This was a retrospective study based on analysis of data of consecutive patients referred from 1999 to 2000 to the Allergy Clinic of the University of Bari, reported to have experienced episodes of urticaria and/or angioedema after ingesting meals or products containing tartrazine during the previous 10 days before the first visit and submitted to a challenge test with tartrazine (Table 1).

In all cases, the skin reactions had been diagnosed by a doctor, and all patients provided a medical report detailing the adverse reaction.

Patients' clinical data and test results were collected in a database used for this study (EPI INFO 6 software, Division of public health surveillance and informatics, WA, USA).

At the first visit to the outpatients clinic, a careful anamnesis had been taken, including a detailed questionnaire with special attention to the reported hypersensitivity-type reaction (a description of the symptoms, any concomitant drug therapy, any treatment with antihistamines or other

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Table 1. Characteristics of the 102 patients investigated

	No. (%)
Sex (M/F)	34/68
Mean $\pm$ SD	38.5 $\pm$ 11.6
Age distribution (years)	18–66
<i>Clinical features of reported adverse reaction</i>	
Urticaria	61 (59.8%)
Angioedema	2 (1.9%)
Urticaria/angioedema	39 (38.2%)
<i>Accompanying symptoms</i>	
At least one symptom	31 (30.4%)
Nausea	14 (13.7%)
Headache	3 (2.9%)
Nasal congestion	8 (7.8%)
Respiratory difficulty	11 (10.8%)
Atopy	20 (19.6%)
<i>History of drug hypersensitivity</i>	
Urticaria	10 (9.8%)
Asthma	4 (3.9%)
Erythema multiforme minor	2 (1.9%)
Anaphylactic shock	1 (1%)
<i>History of food hypersensitivity</i>	
At least one positive reaction to an IgE test with food extracts	24 (23.5%)

drugs). During the anamnesis, any history of atopy (atopic dermatitis, asthma and rhinoconjunctivitis), or of drug and food hypersensitivity was enquired about.

Patients had then been instructed about further diagnostic tests. To exclude the possibility of a positive reaction to the challenge resulting from the ingestion of a food additive other than tartrazine or a food that has been reported as a potential cause of urticaria, patients had been instructed to follow an additive-free diet and an oligoantigenic diet for a minimum of 7 days before the challenge [3].

Daily, before testing, the patients were asked to come back to the Allergy Clinic to verify that they were correctly following the diet, that they were not taking antihistamines for at least 7 days before challenge (4 weeks in the case of astemizole), and no drugs of any type for 48 h before testing. In addition, it was daily verified whether patients were presenting any symptoms.

IgE tests

Skin prick tests (SPTs) were performed with common inhalant allergens (Bayropharm, DHS, Milan, Italy). SPTs were performed with a panel of common food-allergen extracts (Bayropharm) and other allergens were used as appropriate. Skin prick tests were performed according to Pepys' method [4] using histamine (10 mg/mL) and normal saline as positive and negative controls, respectively. Weals of 3 mm or greater were regarded as positive in the absence of a reaction to normal saline.

Concentrations of serum-specific IgE to food allergens were determined by fluoro enzyme immunoassay (FEIA) with the Pharmacia CAP System under standardized conditions, as recommended by the manufacturer (Pharmacia, Uppsala, Sweden). A positive RAST was defined as a value >0.35 kU/L.

Challenge to tartrazine

After obtaining written informed consent from all subjects, a challenge to tartrazine (E102) had been performed. Resuscitation equipment was available during all challenges. None of the patients presented symptoms at the time of testing. Patients had not been taking antihistamines for at least seven days before peroral challenge (4 weeks in the case of astemizole), and no drugs of any type were used 48 h before testing. The patients continued the elimination diet throughout the entire challenge period. At the time of testing, patients had no significant active medical conditions (of a pulmonary, gastrointestinal, cardiovascular, psychiatric, hepatic, neurologic, renal or haematologic nature), and women were not pregnant.

Challenges were administered using a double-blind placebo-controlled procedure (DBPC) during the morning hours. No food was ingested as from midnight on the previous day and for 2 h after the challenge. The challenge procedure lasted 5 days: on day 1, patients received a challenge with placebo opaque capsules (talc). If no symptoms were noted after placebo, a DBPC was performed after 48 h.

During the challenge test, subjects randomly received placebo on day 3 and tartrazine on day 5 (after a washout day), or tartrazine on day 3 and placebo on day 5 (after a washout day).

Tartrazine and placebo (talc) were given in an identical opaque capsule; patients received an equivalent number of placebo and tartrazine doses. Tartrazine was given at increasing dosages: 5, 10 and 20 mg. Each dose was given after 2 h, if no symptoms had developed with the previous administration.

Vital signs such as arterial blood pressure, heart rate and respiratory rate were monitored before, during and after the challenge procedure. In patients with histories of rhinitis and/or bronchial asthma, the forced expiratory volume in 1 s (FEV₁) was also measured.

Subjects were monitored at all times for possible urticaria or angioedema and any other adverse symptoms. The nature, onset, duration, severity and resolution of all adverse experiences were recorded. Only the appearance of urticaria (defined as pruritic and erythematous areas raised over normal skin) and/or angioedema (defined as swelling of the skin and/or external mucosa) was considered as a positive response. Provocation was stopped if clinical symptoms were observed or the highest dose was reached. At the end of the study, the contents of the capsules (tartrazine and placebo) were verified. The patients remained at the allergy centre under controlled conditions for at least 2 h after challenges, and were then asked to come back or call the hospital within 42 h thereafter, so as to exclude delayed reactions. All reactions were followed up and treated until they resolved.

Results

Study group characteristics

A total of 102 subjects were enrolled in the study: 68 (66.7%) subjects were female and 34 (33.3%) were male. Age ranged from 18 to 66 years (mean 38.5 ± 11.6). In this study, atopy was diagnosed by the presence of one or more positive SPT

for common inhalant allergens in patients with a clinical history of allergic rhinoconjunctivitis, asthma or eczema/dermatitis [5]; 20 subjects (19.6%) could be defined as atopic.

Historically, of the 102 subjects enrolled, 61 (59.8%) had experienced only generalized urticaria involving many areas of the body, 39 (38.2%) had experienced both urticaria and angioedema and 2 (1.9%) had experienced angioedema only. All patients denied any concomitant medication use. Thirty-one individuals (30.4%) also experienced one or more other accompanying symptoms including nausea (14 cases), headache (three cases), nasal congestion (eight cases) and respiratory difficulty (11 cases). All episodes of urticaria/angioedema occurred between 1 h and 6 h after consumption of products containing tartrazine. The median duration of the urticaria was 2 and a half hours (45 min to 6 h). Reactions were treated with antihistamines (not astemizole) with or without corticosteroids.

In 75 subjects (73.5%), the urticaria could be defined as acute, while in the remaining 27 subjects (26.5%) it could be defined as episodic [6], because in addition to the last episode, they had experienced other sporadic episodes of urticaria that might be related to tartrazine.

Fourteen subjects (13.7%) also reported having experienced drug hypersensitivity to non-steroid anti-inflammatory drugs and antibiotics: the reactions consisted of urticaria in 10 cases, asthma in four, erythema multiforme minor in two, and anaphylactic shock in one patient. Among the 14 drug-hypersensitive patients, two (2/102; 1.9%) experienced acetylsalicylic acid (ASA) hypersensitivity: one subject experienced urticaria, the other experienced asthma. Fifteen (14.7%) patients reported a history of food hypersensitivity.

IgE tests results to food allergens

Twenty-four subjects (23.5%) showed at least one positive reaction to an IgE test for food allergy: wheat (eight positive reactions); corn and almond (seven to each); bean and soybean (six to each); filbert (five reactions); peach and eggs (four reactions to each); yeast, oat and *Anisakis simplex* (three to each); milk, melon, strawberry, peanut, codfish; shrimp, barley (two to each); pea, tomato, chicken, tuna, potato, walnut, orange, apple, celery, salmon, lobster, crab (one to each).

Challenge results

The challenge was performed within a range of 10–21 days after the urticaria had settled down.

Only one subject (1%) had reactions on day 5 after ingestion of 5 mg of tartrazine. She did not have adverse reactions to placebo. The remaining patients did not show reactions after the ingestion of placebos or tartrazine and vital signs remained stable, showing only slight non-significant variations.

The patient with a positive reaction was a 19-year-old without a personal history of atopy or drug and food hypersensitivity. IgE tests with food and inhalant extracts were negative. Before testing, the patient had last taken her meals at 20:30 hours and she had eaten rice and olive oil. Fifteen minutes after the ingestion of the first dose of tartrazine, the patient developed facial swelling, and pruritic

and urticarial lesions on the trunk and extremities. In addition, she experienced nausea and abdominal pain and became mildly hypotensive (blood pressure dropping from 120/80 to 90/70).

Her symptoms and signs subsided within a few hours after the administration of antihistamine, corticosteroids and epinephrine.

Discussion

Tartrazine has been frequently linked to different illnesses such as chronic urticaria (CU) and asthma [7–12]. In addition, cases of angioedema, of purpura, exacerbation of atopic dermatitis and gastrointestinal symptoms related to tartrazine have been reported [13–16]. However, a cause-and-effect role for tartrazine in these illnesses, especially in urticaria, has not been established. In fact, these studies could be criticized for several reasons: in some, no reference is made as to whether medication, particularly antihistamines, was continued or withheld during challenges [7, 8, 17], while in some studies the challenge procedure used was a single-blind test, introducing a grave risk of observer bias [18, 19].

Moreover, there are a number of published studies in which placebo was not utilized. These studies are useless as a means of linking the response specifically to a challenge substance [19, 20]. Instead, in most placebo-controlled studies, the placebo was usually the first challenge substance followed by tartrazine. In this case, a spontaneous flare of urticaria, for instance, was least likely to coincide with the first placebo challenge, particularly if antihistamine was last ingested just before beginning challenges. The use of multiple placebos, including randomization of placebos, enhances the design of challenges and eliminates the risk of bias previously quoted [9, 21].

In addition, some studies used a mixture of colourings in the challenge so that the positive reactions cannot be reliably attributed to any one substance, including tartrazine [14] and the criteria according to which the authors judged a reaction as positive were not always clearly illustrated.

In this study, we focused our attention on the rule of tartrazine in acute urticaria, while several other studies focused their attention on the rule of tartrazine and other additives in various types of urticaria.

In CU, as mentioned above, non-allergic hypersensitivity reactions to food additives have been repeatedly reported. The incidence of any reactions to additives in patients with CU is unknown; this is because of the lack of rigorously controlled studies and inherent problems in challenging patients with CU. One of the earliest open additive challenge studies in CU patients was reported by Doeglas [22]. He found that 30.4% of patients reacted to tartrazine and 17.4% reacted to sodium benzoate. Subsequently, Thune et al. [19] found that 62% of patients with CU reacted to at least one of the 22 different additives used in challenges. Genton et al. [17] performed single-blind additive challenges on 17 patients with CU. He found that 88.2% developed urticaria after at least one of the six additives used for challenge. Goodman et al. [23] reported two patients who had exacerbation of their urticaria after challenge with butylated hydroxyanisole

(BHA) and butylated hydroxytoluene (BHT). Recently, using a rigorous protocol, Asero [24] demonstrated a case of CU correlated with the ingestion of monosodium glutamate.

Other studies have denied the role of additives in the exacerbation or aetiology of CU. These papers include the one by Hannuksela et al. [25], in which 44 CU patients were challenged with several food additives. Only one had a positive challenge, although one other patient reacted to a placebo challenge. Kellet et al. [26] noted that about 10% of CU patients reacted to tartrazine and/or sodium benzoate, but 10% of the same subjects also reacted to placebo.

Enormous importance should be paid to the urticarial activity; in fact, discontinuation of antihistamines by CU patients before challenging could induce false-positive reactions, so it is difficult to understand whether the reaction is truly causally related or is a spontaneous exacerbation of the urticarial process, especially when a rigorous protocol has not been used (careful anamnesis, additive-free diet, multiple randomized placebos). Instead, continuation of antihistamines during challenges may block some of the milder additive-induced cutaneous responses and therefore promote false-negative results.

Additives are also linked to the occurrence of acute or episodic urticaria/angioedema, although these cases have been less extensively investigated. In particular, naturally occurring dyes, such as carmine, have been associated with episodic and acute urticaria/angioedema through an IgE-mediated mechanism [27]. Geha et al. [28] conducted a study on individuals with a history of urticaria after ingestion of an aspartame-containing product. By means of DBPC challenges, the authors demonstrated that aspartame is no more likely than placebo to cause urticaria/angioedema in these subjects: they observed four reactions, two of which followed aspartame ingestion and two placebo ingestion.

Several studies have investigated 'cross-hypersensitivity' between ASA and tartrazine, especially among asthmatic patients. Initially, ASA and tartrazine intolerance was assured because of a similarity between the chemical structures of ASA and a portion of the tartrazine structure. In the early studies, cross-reactivity between ASA and tartrazine was estimated to occur in between 21% and 100% of aspirin-sensitive patients [21]. In the course of years, several studies were carried out, but a review of the literature yields discordant results. In fact, in different studies, different percentages of cross-reactivity reactions were found. Different studies used different protocols: single-blind vs. double-blind, different dosages of tartrazine, different criteria to define a positive reaction. In some studies, the percentage of cross-reactions was high (15.9%, 25%) [29, 30]. In our study, the percentage of patients who reported a history of ASA hypersensitivity was very low, and the only proven tartrazine-sensitive subject did not refer any such history. Thus, we agree with some authors who proposed that cross-reactivity between tartrazine and ASA may be rather due to the deprivation of drugs such as bronchodilators before testing or could depend on the high prevalence of unstable airways in the asthmatic population afflicted with aspirin disease [21].

This study shows that the percentage of acute urticaria and/or angioedema induced by tartrazine is very low, despite the fact that all individuals enrolled in this study experienced an adverse reaction that could have been related to ingestion of

this food additive. Based on a rigorous protocol (DBPC with multiple placebos), we demonstrated that only 1% of subjects incontrovertibly had an adverse reaction to tartrazine.

In this study, we have estimated the quantity of tartrazine that might have been consumed by patients on the basis of the technical leaflets of products, whenever possible, in addition to the reported data from the European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuff. The mean estimated intake of tartrazine was reported by the Commission on Dietary Food Additive Intake in the European Union as 7.5 mg/kg. In this study, the dosage tested is lower than that ingested in a normal diet.

From an analysis of the results it is evident that 19 (18.6%) patients showed at least one clinically relevant positive reaction to an IgE test for food allergy. Some of these confirmed previous findings in patients with a history of food hypersensitivity, while the other positive reactions suggest that patients reacted to the food ingested rather than to tartrazine. However, in all cases, we can consider the 19 positive subjects as food sensitive and not as food allergic because we have not confirmed the positive IgE test results by food challenges. In the remaining 81.4% of subjects without food sensitization, the origin of the urticaria or angioedema attack remains unknown. However, it is reasonable to suppose that many reactions reported as food allergy are non-immunological, although clinically similar to IgE-mediated reactions. In this circumstance only oral food challenges, and not SPTs or RAST could identify the specific food. In addition, in some subjects, the adverse reaction could be against other commonly used food additives contained in the ingested products, not challenged in this study. In fact, as shown in our study, no patients showed any symptoms during the additive-free and oligoantigenic diet, while only one reacted to tartrazine. This fact leads us to think that, excluding food-induced urticaria/angioedema, some reported episodes of urticaria/angioedema could be caused by the ingestion of other additives, not allowed during the diet period. Finally, there are cases where there is no specific antigen known to cause urticaria/angioedema episodes, and the disease could be considered to be a disease of unknown origin ('idiopathic').

In this study, in agreement with other authors [28], patients' history was a poor indicator of a possible additive hypersensitivity because patients are usually unaware of all the additives that they consume daily and because the same product could contain more than one additive. In view of our results, we suggest that all physicians with patients who have suffered adverse reactions that could be attributed to tartrazine should also carefully evaluate other possible causes.

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