Allergy to Tartrazine in Psychotropic Drugs

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Background: High psychiatric morbidity has been reported among those who complain of food intolerance or allergy. Many cases of food allergy or intolerance to drugs are not due to allergy to the food or drugs themselves, but to the additives used for coloring, flavoring, preserving, thickening, emulsifying, or stabilizing the product. Of various coloring dyes used, tartrazine (FD & C yellow no. 5) is the color most frequently incriminated in producing allergic reactions. The exact epidemiology and pattern of allergic reactions to tartrazine in psychotropic drugs have not been frequently studied and reported.

Method: The present study included consecutive outpatients (May 1996 to April 1998) who developed allergic reactions or intolerance to tartrazine in psychotropic drugs. Total patients exposed to tartrazine-containing drugs were also recorded. The subjects showing allergic reactions to tartrazine were then exposed to non–tartrazine-containing brands.

Results: Of 2210 patients exposed to tartrazine-containing drugs, 83 (3.8%) developed allergic reactions. The symptoms subsided within 24 to 48 hours of stopping the drug. None of the patients showed allergy to non–tartrazine-containing brands. History of allergy to tartrazine was present in 13.2%, and 15.7% of patients had a history of aspirin sensitivity.

Conclusion: Tartrazine allergy should be considered in patients developing drug allergy, because it would require changing the brand rather than stopping treatment with that drug.

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The relationship between psychological and allergic disorders is still a scientific controversy. A variety of hypotheses linking the two have been put forward,[1] but demonstrating any association has been difficult. Particularly, high psychiatric morbidity has been attributed to those who complain of food intolerance or allergy and who attend allergy clinics.[2] Many cases of food allergy or intolerance to drugs are not due to allergy to the food or drugs themselves but to the additives used for purposes of coloring, flavoring, preserving, thickening, emulsifying, or stabilizing.[3–5] Some of these chemicals are similar to or cross-react with drugs. During the course of a year, it is estimated that every person in the world consumes chemical substances that are not normal constituents of food, and the quantity of those substances is increasing.[6] The total number of known food additives exceeds 20,000.[6] Food additives are controlled by law in most countries, although thousands have not been subjected to double-blind trials for adverse reactions. The potential hazard of intake of these additives must be seriously considered because of extensive and prolonged use of these agents in the diet.[4]

Drug allergy is defined as a state of hypersensitivity induced by exposure to a particular drug that results in harmful immunologic reactions. Drug allergy comprises an important proportion of medical practice. Besides the main ingredients, individual intolerance and idiosyncratic reactions may occur to chemical agents present in the prescribed drug.[7] These reactions may inadvertently be attributed to the main drug, which is then incorrectly stopped, thus depriving the patient of the benefits of an important effective drug.

Out of various coloring dyes used (Table 1), tartrazine (FD & C yellow no. 5) is the color most frequently incriminated in producing allergic reactions.[3,8–10] In foods such as colored candy, desserts such as puddings, pastry frostings, salad cream, custard powder, sweets, marzipan, jam and marmalade, smoked cod and haddock, mustard, dry drink powders such as Tang, carbonated drinks, and colored sweets and as a dye to color certain proprietary drug capsules, toothpastes, and many cosmetics, tartrazine is present in significant quantities.[9] Most individuals ingest tartrazine on a daily basis, and many diets contain up to 5 mg of tartrazine daily.[9]

Tartrazine is a coal-tar derivative with a similar chemical structure to the benzoates, other azo compounds, pyrazole compounds, and the hydroxyaromatic acids, which include salicylates. It shows relatively little protein binding in comparison with non-azodyes[11] and may require prior metabolism before it can induce an immune response. The azogroup can be reduced in the intestine and liver,[12] one of the several routes through which the compound could be conjugated to form a potentially antigenic hapten structure.[13] Studies have shown that clinical hypersensitivity to tartrazine may be associated with a humoral immune response to part of the molecule, namely, its sulfophenyl

Table 1. Common Food and Drug Additives Causing Allergic Reactions[a]

Flavoring Agents	Coloring Agents
Aspartame	Amaranth (Red no. 2 dye)
Cyclamate	Tartrazine (FD & C yellow no. 5)
Quinine	Phenolphthalein
Cinnamon oil	Brilliant blue (FD & C blue no. 1)
Vanilla	Erythrosine (FD & C red no. 3)
Salicylates	Indigotin (FD & C blue no. 2)
	Ponceau (FD & C red no. 4)
	Sunset yellow (FD & C yellow no. 6)
	Quinolone yellow
	Indigocarmine
	Chocolate brown HT
	Carmoisine
	Pigment rubine
	Sodium benzoate
	Monosodium glutamate
	Sodium metabisulphite

[a]Reactions include acute or chronic urticaria and, rarely, purpura or asthma.

antigenic determinants.[13,14] The exact mechanism of the adverse reaction to tartrazine is not known.

Intolerance to tartrazine was first reported in 1959,[15] and its part in the induction of intractable urticaria has been recognized since 1975.[16] According to classification of adverse food reactions,[17] reactions to food additives can be caused by allergic, substance-specific immunologic mechanism. Nonthrombocytopenic purpura is also reported to be due to hypersensitivity to tartrazine, which suggests the possibility that tartrazine may act as a hapten bound to the endothelial cells of small blood vessels.[18–20]

The present study was conducted to detect patients who developed allergic reactions to tartrazine in psychotropic drugs.

METHOD

The study was carried out for 2 years (May 1996 to April 1998) in the psychiatry outpatient department of a tertiary care teaching hospital (New Delhi, India). All the cases developing allergic reactions to drugs were included in the study.

Detailed history and physical examination of the patients presenting with allergic reactions associated with administration of tartrazine-containing brands of psychotropic drugs were recorded. The patients had been diagnosed with schizophrenia, mania, depression, generalized anxiety disorder (5 patients also had panic attacks), and sleep disorder according to DSM-IV criteria. The patients with a history of organic brain syndrome, drug abuse, or intake of any other medication except psychotropic drugs were excluded. Those patients receiving more than one psychotropic medication with different coloring agents, taking one drug with more than one coloring agent, or taking a drug without complete information about the coloring agent were excluded. The diagnosis of tartrazine-induced allergic reaction was made from the confirmed history of intake of tartrazine-containing psychotropic drug, development of allergic reactions (pruritus and/or rash or other allergic symptoms diagnosed with the help of a dermatologist or a physician), stoppage of tartrazine-containing brands, and disappearance of allergic reactions after stoppage indicating improvement. These patients were then shifted (after a 2-week period without the drug) to non–tartrazine-containing brands. The patients did not develop allergic symptoms to the new brands, thus ruling out allergy to drug rather than the dye. Information collected during the study period included the composition of brands, dosage, reactions and type, and outcome. The type of urticaria and the severity were, however, not recorded.

Table 2. Distribution of Total and Study Cases[a]

Drug	Total Number of Patients Receiving Psychotropic Drugs Containing Tartrazine	Patients Who Developed Urticaria	%
Neuroleptics			
Haloperidol	188	6	3.2
Trifluoperazine	145	3	2.1
Chlorpromazine	92	5	5.4
Penfluridol	48	3	6.3
Pimozide	22	1	4.5
Antidepressants			
Imipramine	130	9	6.9
Amitriptyline	46	4	8.7
Clomipramine	27	2	7.4
Anxiolytics and hypnotics			
Alprazolam	1360	42	3.1
Buspirone	62	4	6.5
Chlordiazepoxide	22	1	4.5
Nitrazepam	68	3	4.4

[a]Of the total 2210 patients, 83 (3.8%) developed urticaria.

RESULTS

Eighty-three (3.8%; 50 women, 33 men; age, 18–55 years; known allergy to other drugs in 11 patients) of the 2210 patients exposed to tartrazine-containing psychotropic brands developed allergic reactions. The distribution according to the drug type appears in Table 2.

The most common allergic reactions were pruritus and rash, appearing within 1 week of drug intake. Of the 83 patients who developed allergic reactions to tartrazine-containing psychotropic drugs, 77 (92.8%) experienced pruritus and rash. The other symptoms were rhinorrhoea, watery lacrimation, cough, hoarseness, wheezing, and dyspnea. Restlessness was reported by 52 (62.5%) of 83 patients, although it did not interfere with sleep. The allergic symptoms subsided within 24 to 48 hours of stopping the offending brand. Six patients were also prescribed antihistamines for 1 week. All the patients were prescribed non–tartrazine-containing brands after a 2-week

washout period. None of the patients developed the allergic reactions again. Four patients who again received the tartrazine-containing brands (owing to substitution of brand by the pharmacist) again developed the similar symptoms within 24 hours. Thirteen patients had a history of aspirin sensitivity, but they did not differ from patients who developed tartrazine-induced allergic reactions and were aspirin nonreactors.

The average dosage of tartrazine-containing drugs in patients developing allergic reactions did not differ from that in those without these reactions. The presentation of reactions was relatively similar with all the tartrazine-containing drugs.

DISCUSSION

Since allergic reactions occurred when patients took tartrazine-containing brands but not when they took other brands, allergy to tartrazine appears to be the most likely explanation in these cases. Allergic reactions to tartrazine and other dyes have been reported to occur in 0.6% to 2.9% of persons, but in the present series, 3.8% of persons taking tartrazine-containing psychotropic medication developed allergic reactions. The incidence of tartrazine sensitivity has been reported to be higher in asthmatic or allergic subjects than in the general population. The tartrazine-containing drug that produced the most frequent allergic reactions was amitriptyline (8.7%), followed by clomipramine (7.4%), imipramine (6.9%), and buspirone (6.5%). The pattern of allergic reactions to tartrazine in various psychotropic drugs has not been reported.

Allergic reactions to tartrazine have been reported more frequently in people with aspirin sensitivity,[21–25] but the exact prevalence is not known. Although patients have similar pathologic reactions to tartrazine and acetylsalicylic acid, no effect of tartrazine on inhibition of prostaglandin pathways has been observed,[22] indicating that different biological pathways are involved. Only a few reports mention tartrazine sensitivity without aspirin intolerance,[9,26] or aspirin intolerance without tartrazine intolerance.[27,28] The average dosage (mean as well as range) of psychotropic drugs used in patients developing allergic reactions to tartrazine did not differ significantly from that in patients without these reactions. The presentations of allergy to tartrazine were relatively similar in all the tartrazine-containing psychotropic drugs. It is suggested that tartrazine, sodium benzoate, monosodium glutamate, and sodium metabisulfate all have an effect similar to that of aspirin and other salicylates in the inhibition of thromboxane B_2 formation by norepinephrine-activated platelets.[29]

In the present study, the common pattern of allergic reactions to tartrazine included pruritus and rash (urticaria), asthma, rhinitis, angioedema, nonthrombocytopenic purpura, marked restlessness, and anaphylaxis. These reactions, except marked restlessness, have also been previously reported in other studies.[18,21,30–32] The high incidence of restlessness (62.5%) found in the present study is significant because dietary factors (preservatives and artificial coloring agents) have been reported to play a significant role in the etiology of the majority of children with attention-deficit/hyperactivity disorder.[33,34]

Further research is required into basic mechanisms and the epidemiology of the conditions provoked by tartrazine. Only then can the hazard of tartrazine be properly evaluated. People sensitive to acetylsalicylic acid and those who are also allergic to foods should avoid tartrazine as a food or drug dye. Medical practitioners need to know which brands contain the dye so that they do not prescribe them for their dye-sensitive patients and instead use other alternative brands. Each and every drug formulation should mention the name of the dye or the coloring agent (rather than just mentioning "coloring agent-quantity sufficient") along with the precaution "subjects sensitive to tartrazine should avoid this preparation." Since many of the pharmaceutical companies in developing countries do not mention tartrazine or other coloring agents in their package inserts, the treating doctors should keep in mind that the patients who develop allergic reactions to a preparation may have developed them owing to the coloring agent rather than the drug itself. This will help by not depriving the patient of a useful and effective drug.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), buspirone (BuSpar), chlordiazepoxide (Librium and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil and others), haloperidol (Haldol and others), pimozide (Orap), trifluoperazine (Stelazine).

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