

A combined single-blind, double-blind, placebo-controlled study to determine the reproducibility of hypersensitivity reactions to aspartame

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Aspartame is an o-methyl ester composed of phenylalanine and aspartic acid. After its final approval as a sweetener in 1981, a number of reports of adverse reactions to aspartame appeared in the literature. To explore the pathogenesis of such reactions, we initiated a study in July 1986 to identify subjects with hypersensitivity reactions to aspartame with blinded challenge procedures. The study was closed after 32 months. During that time, we advertised in local newspapers and worked closely with the local community of allergists and dermatologists in an attempt to recruit subjects with hypersensitivity reactions to aspartame. A total of 61 self-referrals and physician referrals were screened, with 20 referrals evaluated in clinic. After this evaluation, 12 patients underwent single- and double-blind challenge with up to 2000 mg of aspartame. No subject with a clearly reproducible adverse reaction to aspartame was identified. In summary, we found that it is difficult to recruit study subjects with a history of hypersensitivity reactions to aspartame and that subjects who believed themselves allergic to aspartame did not have reproducible reactions. (J ALLERGY CLIN IMMUNOL 1991;87:821-7.)

Aspartame is an o-methyl ester composed of phenylalanine and aspartic acid. It was discovered serendipitously in 1965 by a chemist working to find an inhibitor of gastrin with possible applications as an antiulcer agent.¹ In 1973, G. D. Searle petitioned the FDA for its approval to market aspartame as a sweetener.² In 1974, aspartame was approved for use in dry foods. In December 1975, the FDA stayed the approval for marketing aspartame because of concern over problems noted in studies by Searle Laboratories (Chicago, Ill.) and because of allegations that aspartame was unsafe and could cause mental retardation and endocrine dysfunction. In July 1981, the FDA Commissioner reapproved aspartame as a food additive, and marketing was started that same year. In July

Abbreviations used

FDA: Food and Drug Administration
NIH: National Institutes of Health
DKP: Diketopiperazine

1983, aspartame was approved for use in carbonated beverages.³

Since its discovery, during the approval process, and after marketing occurred, there have been several reports of adverse reactions. Reports of allergic reactions to aspartame include those reported to the Centers for Disease Control and occurring between 1982 and 1984. Of 199 patients reviewed in depth, 65 had symptoms considered classic for food allergy, including gastrointestinal distress, urticaria, rhinitis, and wheezing.⁴ There have been two case reports of aspartame-induced urticaria reproduced by double-blind challenge,⁵ and one report of granulomatous panniculitis.⁶ Other investigators have addressed the issue of aspartame and sensitivity to headaches⁷⁻⁹ as well as safety issues.^{10, 11} Because of the Centers for Disease Control reports of allergic reactions to aspartame and the report of reproduction of aspartame-associated urticarial reactions by double-blind chal-

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TABLE I. Problems reported by respondents to arise from aspartame consumption

No. of patients	Symptoms*
16	Headaches
16	Hives
5	Diarrhea
5	Dizziness
4	Seizures
3	Rhinitis
3	Shortness of breath
2	Abdominal discomfort
2	Cramping, menstrual bleeding, vaginal itching
2	Anaphylaxis
1	Numb hands and feet
1	Hyperreactivity
1	Blindness, intermittent
1	Sexual urges
1	Nightmares, depression
1	Flu-like syndrome, "dopiness"
1	Basal cell carcinoma
1	Difficulty swallowing
1	Itching, no rash

*Sixty-seven complaints in 61 patients.

lenge, we designed a protocol to examine aspartame-associated hypersensitivity of "allergic" reactions. The protocol spans a period of 32 months, from July 1986 to February 1989. During this time, multiple efforts to recruit patients sensitive to aspartame were made through local newspapers and the local medical community. This article details the results of this effort.

MATERIAL AND METHODS

Subjects

We advertised for individuals who believed they might be sensitive to aspartame four times in the NIH Record (circulation 1800) and five times in the *Washington Post* Health Section (circulation 781,000) during the duration of the protocol. A typical *Washington Post* advertisement under the volunteers listing in the Health Section was: "National Institutes of Health seeks normal volunteers and people who get hives and other allergic reactions from products containing Nutrasweet and who are between 18 and 50 to participate in a study of aspartame (NutraSweet). Call Dr. Margarita Garriga: (Tel. no.)." The local community of allergists and dermatologists were informed of the protocol, both by letter and during local meetings, and asked for help in referring patients they believed had a problem with aspartame sensitivity. Members of the Washington, D.C. Allergy Society and the Washington, D.C. dermatology group received such direct mailings. Announcements of the protocol were posted on bulletin boards at NIH and in local hospitals. Letters and announcements were full page and

included information on where aspartame could be found and listed a full spectrum of possible allergic reactions. Subjects who experienced various adverse reactions contacted us by telephone. Subjects with complaints of a possible allergic nature were referred for a clinic visit to determine if they were candidates for aspartame challenge.

Volunteers had no history of reactions to aspartame and included normal (one male and four female volunteers) and atopic (four female and two male volunteers) subjects ranging in age from 27 to 42 years. Both volunteers and subjects with a history of allergic reactions associated with aspartame ingestion were entered into the study after informed consent (NIH protocol No. 86-1-09).

Laboratory studies

Skin testing was performed by the prick skin method to various aeroallergens, including ragweed, grasses, trees, molds, mites, and dust, and *Aspergillus*; some foods, including peanuts, crab, cod, cows' milk, egg white and egg yolk, fish mix, lobster, pecans, scallops, sesame, shrimp, and tuna; and aspartame, DKP, monosodium glutamate, and sulfites. All allergen extracts and additives were prepared in a suspension with glycerol-saline 1:20 wt/vol except aspartame, which was prepared with glycerol-saline 1:100 wt/vol. Histamine (1 mg/ml) and glycerinated saline served as positive and negative controls, respectively. On evaluation at 15 to 20 minutes, those skin test sites with a net wheal diameter that was ≥ 3 mm larger than the wheal diameter at the negative control site were considered positive.

A complete blood count with differential, glucose, electrolytes, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, calcium, blood urea nitrogen, creatinine, and cholesterol, and quantitative IgG and IgE were performed on all subjects. Plasma histamines were determined with a modification of a single isotope radioenzymatic assay in which histamine was radiolabeled with a tritiated methyl group by *N*-methyl transferase and subsequently determined as H_1 methylhistamine by thin-layer chromatography (upper 95% confidence limit for normal subjects, 617 pg/ml).¹² Appropriate tests were completed to determine if the patient had a physical disorder that might explain a complaint of "food allergy" or the reported sensitivity to aspartame.

Challenge procedure

Oral aspartame challenges were performed on subjects who were between the ages of 18 and 65 years, including normal and atopic volunteers as well as individuals with suspected hypersensitivity reactions to aspartame. Adverse reactions considered were nausea, difficulty swallowing, vomiting, abdominal pain, diarrhea, abdominal distention, flatulence, urticaria, angioedema, pruritus, cutaneous flushing, eczema, rhinitis, asthma, hypotension, syncope, and headache. Only headaches that met the standard criteria of an immediate hypersensitivity reaction (within minutes to 1 hour, reproducible with each exposure) were considered. Pregnant women and individuals with significant cardio-

vascular, neurologic, pulmonary, renal, or gastrointestinal diseases were excluded by the protocol.

The aspartame challenge consisted of administration of placebo (lactose) or food-grade aspartame (G. D. Searle, Co., Chicago, Ill.) in opaque capsules. The patient observed an overnight fast before challenge. Antihistamines were stopped for at least 72 hours before challenge. No patients were receiving steroids, β -agonists, or long-duration antihistamines in proximity to study. The subjects were seated in a clinic room with an intravenous line in place. In patients with a history of severe reactions, the capsules were administered while the patient was under a doctor's close supervision. The capsules were administered in a single-blind manner to both control subjects and patients suspected of having aspartame-induced hypersensitivity reactions. This challenge procedure was performed with increasing dosages of aspartame (0, 10, 100, 500, 1000, and 2000 mg) at 30-minute intervals or at intervals that exceed the reaction time reported by history. Before each dose, or with a reaction, blood was collected in a purple-topped tube (containing heparin) and immediately placed on ice (later to measure plasma histamine). The FEV₁ was obtained before each dose or with a reaction with a Panasonic multispiro PC machine (Senior Partner).

A positive challenge was defined as reproduction of the historical complaint, an obvious allergic reaction (hives, edema, flushing, vomiting, diarrhea, and hypotension), or a decrease in FEV₁ $>20\%$. (A change of 20% or less was considered within normal limits in relationship to aspartame administration.) Patients who had a positive response (not life-threatening) were next examined no sooner than 2 weeks later in a double-blind, placebo-controlled fashion, receiving either five capsules of aspartame (2000 mg) or five capsules of placebo followed by the alternative regimen in which the number of placebo capsule challenges approximated the number of aspartame-containing capsule challenges. Patients who had no response to aspartame capsules were administered an aspartame-containing diet soda.

RESULTS

Through the various recruitment efforts, we received a total of 61 phone calls. Initial symptoms reported by respondents are detailed in Table I. Of these calls, 19 had complaints that were not considered due to immediate hypersensitivity reactions to aspartame (e.g., anxiety, depression, menstrual abnormalities, and intermittent blindness). Six individuals were excluded because of an underlying disease that prevented entry into our protocol (one with thyroid disease, two with seizures, one with lupus, and hypertension, one with heart block, and one individual receiving therapy for depression). In three individuals, complaints attributed to aspartame did not always occur after aspartame ingestion. Eleven potential subjects rejected the idea of being studied, saying that their problem was too minor to justify the time involvement (Fig. 1). Not illustrated in Fig. 1 are a

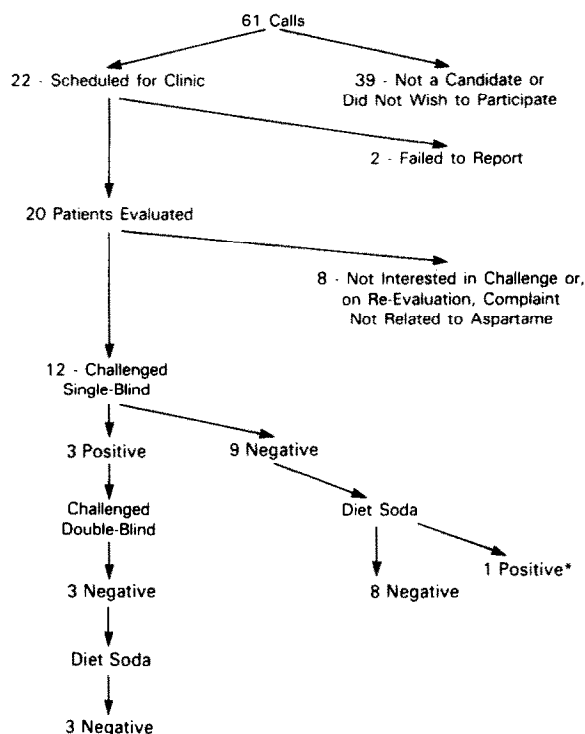


FIG. 1. Disposition of aspartame-related calls and outcome of recruitment and challenge; * questionable positive reaction (see text).

number of calls from people who were interested in what adverse reactions aspartame might cause or who wanted to be paid to be studied. One person, for instance, said he was not sure if he ever had a flu-like syndrome from aspartame but, if we paid him to undergo challenge, he would know. Twenty-two subjects were scheduled for clinic. Two patients failed to report. When they were called, they stated they were no longer interested in participating in the study because their suspected problems were not significant enough to warrant participation.

Demographically, the volunteers and patients evaluated in clinic were of similar ages and education. There were three men and eight women in the control (normal and atopic) group and eight men and 12 women in the suspected aspartame-sensitive group (Table II) screened in clinic.

Initial laboratory tests in the control group were largely unrevealing. We did note, for instance, one elevated plasma histamine value before challenge in one atopic volunteer and an elevated IgE in a second atopic volunteer. Five of 11 control subjects had positive skin tests to one or more extracts. As was anticipated, no normal volunteer had an adverse reaction to aspartame or the challenge procedure itself. Pulmonary function tests remained unchanged. More im-

TABLE II. Demographic characteristics of suspected aspartame-sensitive patients evaluated in clinic

Patient No.	Age (yr)	Sex	Occupation	Symptoms attributed to aspartame
1	37	F	Lawyer	Dizziness
2	37	F	Accountant	Bloating Headaches
3	38	M	Administrator	Tinnitus, dizziness
4	29	F	Student	Hives, anaphylaxis
5	28	M	Computers	Rhinitis
6	51	M	Administrator	Headaches
7	28	F	Attorney	Asthma, Hives, gastrointes- tinal upset
8	44	F	Marketing	Headaches
9	42	M	Business	Hives, "welts"
10	29	F	Administrator	Rhinitis
11	32	M	Scientist	Anaphylaxis, hives, asthma
12	15	M	Student	Hives
13	40	F	Administrator	Difficulty swallowing
14	48	F	Psychologist	Hives
15	50	F	Psychologist	Hives
16	45	M	Biomedical engineer	Headaches
17	41	M	Administrator	Hives
18	36	F	Government worker	Diarrhea, flatulence
19	34	F	Program analyst	Rhinitis
20	52	F	Public information	Hives

portantly, plasma histamines remained within the normal range (data not presented).

Of the 20 subjects studied for aspartame sensitivity, IgE was elevated in three subjects (Table III). Eleven of 20 suspected aspartame-sensitive patients had one or more positive skin tests. After initial evaluation of eight of these individuals not interested in challenge or on reevaluation, the complaint was not related to aspartame ingestion. Of the 12 patients with complaints attributed to aspartame and who completed the study, nine patients had negative single-blind challenges (Table IV). One patient (No. 9) developed hives during the single-blind challenge. Two subsequent double-blind challenges were negative. One patient (No. 13) complained of questionable "throat tightness" during single-blind challenge. There were no complaints during double-blind challenge. One patient (No. 19) developed rhinitis during single-blind challenge. Nasal stuffiness and nasal discharge occurred during double-blind challenge both after receiving placebo or aspartame. In all cases, there was no change in blood pressure or pulmonary function tests. Plasma histamine values remained within the normal range.

When patients were challenged with diet sodas, only one patient (No. 2) reacted (twice). Her complaint was feeling bloated and abdominal distention.

She did not react to a regular soda but had this reaction at times when she was not exposed to aspartame.

In summary, no reproducible reactions to aspartame were observed in 12 patients challenged with aspartame complaining of hives alone (Nos. 9 and 20), hives plus anaphylaxis and/or asthma (Nos. 4 and 11), gastrointestinal complaints with or without headache (Nos. 2 and 18), symptoms suggestive of hypotension (No. 3), laryngeal edema (No. 13), headache (No. 6), or rhinitis (Nos. 5, 10, and 19). It should be noted that headache was an infrequent complaint in patients undergoing challenge in that only headache occurring in close proximity to, and clearly related in a consistent fashion to, aspartame ingestion were considered as possibly allergic. Under these specific selection criteria, only one patient (No. 6) with headaches alone was studied, and these did not reproduce. More detailed studies of aspartame and its relationship to headaches are to be found in the literature^{7,9} in which repeated doses of aspartame were administered during usual activity.

DISCUSSION

After the release of aspartame for general use, several studies suggested that aspartame might lead to allergic reactions in some individuals.^{5,6} Particularly

TABLE III. Results of initial tests or subjects suspected of aspartame sensitivity before challenge

Patient No.	Skin tests	Laboratory tests	PFTs	Plasma histamine
1	Plus grasses, ragweed, molds, crab	WNL	ND	ND
2	Negative	WNL	WNL	WNL
3	Plus crab, lobster	WNL	WNL	WNL
4	Plus aspartame, lobster	WNL	WNL	WNL
5	Plus aspartame, dust, mite, <i>Aspergillus</i> , peanut, pecan, soybean, shrimp	↑ IgE	WNL	WNL
6	Negative	↑ Hgb	WNL	WNL
7	Plus dust, trees, ragweed, shrimp, <i>Aspergillus</i> , crab, cod, milk, egg, lobster, peanut, pecan, soybean, sesame, MSG, aspartame, DKP	↑ IgE	ND	ND
8	Plus dust, mites	WNL	WNL	WNL
9	Plus ragweed, grasses, dust, mite, <i>Aspergillus</i> , crab, cod, shrimp, scallop, lobster	↑ IgE	WNL	WNL
10	Negative	↑ BS	WNL	WNL
11	Plus trees, grasses, dust	↑ Uric acid	WNL	WNL
12	Plus ragweed, mold, dust, mite	↑ BS	ND	ND
13	Negative	WNL	WNL	WNL
14	ND	ND	ND	WNL
15	ND	ND	ND	ND
16	WNL	↑ chol	WNL	WNL
17	ND	ND	ND	ND
18	Plus dust	WNL	WNL	WNL
19	Plus trees, ragweed, mold, dust, mite, lobster	WNL	WNL	WNL
20	Negative	WNL	ND	ND

PFTs, Pulmonary function tests; WNL, within normal limits; ND, not done; Hgb, hemoglobin; BS, blood sugar.

intriguing was the study that aspartame could be demonstrated to be responsible for hives in two subjects by double-blind challenge procedures.⁵ Because of these studies, we initiated a study to identify people who believed themselves allergic to aspartame, to reproduce such reactions by double-blind procedures, and to study the pathogenesis of such reactions.

As detailed in this article, after approval of a clinical protocol to study aspartame hypersensitivity, we attempted to recruit aspartame-allergic subjects by repeated newspaper advertisements and interactions with local allergists and dermatologists. This effort resulted in 61 phone calls (Table I) during 33 months. Initial screening was performed to select subjects whose complaints were possibly allergic in nature, and they had appointments scheduled to our clinic.

Our difficulty in recruitment in and of itself we believe to be instructive. If aspartame sensitivity were a common problem, we would have expected more response to our recruitment effort. Previously, with less effort, we successfully recruited patients for study who had immediate reactions to foods.^{13, 14}

Of those respondents selected for clinical evaluation, we thoroughly screened those whose complaints appeared to be allergic in nature. Of these responders, 11 did not wish to take time to participate in the study or to diagnose their condition (Fig. 1). From these 31 responders, six had underlying diseases that made them unsuitable for study (thyroid disease, seizures, lupus, hypertension, heart block, and receiving medication for depression). From the remaining 25 responders, three had symptoms that were not repro-

TABLE IV. Challenge results

Patient No.	Challenge			Results		
	Capsule SB	Capsule DB	Diet soda	Symptoms signs	PFTs	Histamine
2	x			None	WNL	WNL
			x (2)	Bloating*	WNL	WNL
3	x			None	WNL	WNL
			x	None	WNL	WNL
4	x		x	None	WNL	WNL
5	x			None	WNL	WNL
			x	None	WNL	WNL
6	x			None	WNL	WNL
			x	None	WNL	WNL
9	x			Hives	WNL	WNL
		x		None	WNL	WNL
		x		None	WNL	WNL
			x	None	WNL	WNL
10	x			None	WNL	WNL
			x	None	WNL	WNL
11	x			None	WNL	WNL
			x	None	WNL	WNL
13	x			Throat tightness	WNL	WNL
		x		None	WNL	WNL
			x	None	WNL	WNL
18	x			None	WNL	WNL
			x	None	WNL	WNL
19	x			Rhinitis	WNL	WNL
		x		Rhinitis	WNL	WNL
			x	Rhinitis†	WNL	WNL
20	x			None	WNL	WNL
			x	None	WNL	WNL

SB, Single blind; DB, double blind; PFTs, pulmonary function tests; WNL, within normal limits.

*Not considered to be an allergic reaction.

†Rhinitis also receiving placebo.

ducible, leaving 22 of whom two failed to report to clinic and 20 were observed in clinic. Of these responders, one was found unsuitable for study because his headaches were not clearly related to aspartame, and seven decided that they did not want to continue in the study.

Seventeen patients were skin tested to aeroallergens, selected foods, aspartame, and DKP (Table III). Three of these 16 patients (Nos. 4, 5, and 7) had a positive skin test to aspartame,¹⁵ although in each case the reaction was only 4 to 5 mm greater than the reaction at control site. Neither patient 4 or patient 5 had a positive challenge (Table IV). Patient 7 was not challenged. None of the normal subjects had a positive skin test to aspartame. In the absence of a clear and reproducible immediate reaction to aspartame, it is impossible to evaluate the accuracy of skin testing with aspartame in predicting clinical aspartame sensitivity.

Of 11 subjects who had no history of aspartame sensitivity and were challenged, none had a response. Plasma histamines remained unchanged. Thus, the nature of the protocol itself did not yield false-positive results.

We completed challenges in 12 patients (Table IV). We were unable to identify a single patient with a reproducible reaction to aspartame and in whom we could study the pathogenesis of such a reaction. We thus conclude that it is difficult to find and study aspartame-sensitive patients and that, in our series and on blinded oral challenge, symptoms in those patients who believed themselves allergic to aspartame were not reproducible. The failure to identify patients with aspartame sensitivity is consistent with the biology of the aspartame molecule.¹⁶⁻¹⁷ It is a dipeptide, does not appear to act as a hapten, and is rapidly degraded at the brush border. It might thus be expected to rarely induce an IgE response.

Aspartame itself does not directly degranulate mast cells, nor does it enhance the release of mast cells to IgE-mediated stimuli.¹⁵ It does remain possible that aspartame breakdown products induce IgE-mediated responses. This could be the basis for the hives reported associated with aspartame administration. We, however, identified no such individuals. It should be noted that the aspartame used in challenge procedures contains 98% pure aspartame (α -aspartyl-phenylalanine methyl ester) and a small percentage of breakdown products, including 0.17% α -aspartyl-phenylalanine, 0.56% aspartyl-phenylalanine DKP, 0.32% β -aspartyl-phenylalanine methyl ester, and small quantities of other conversion products, such as β -aspartyl-phenylalanine and phenylalanine methyl ester.⁷ This would result in the administration of 6.1, 20.2, and 11.6 mg, respectively, of each breakdown product during the initial single-blind challenge series. No reactions were observed.

We thus conclude that it is difficult in our geographic area to recruit patients with aspartame allergy. This conclusion is based on attempts to recruit subjects and the results of the challenge of 12 individuals. A negative study does not eliminate the possibility that some individuals may become allergic to aspartame. If sensitivity is suspected, avoidance procedures may be initiated. If this is necessary and when this is safe for the patient, aspartame sensitivity can be examined through the application of blinded challenge procedures.

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