# Aspartame is no more likely than placebo to cause urticaria/angioedema: Results of a multicenter, randomized, double-blind, placebo-controlled, crossover study

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**Background:** *Anecdotes and single case reports have suggested that the high-intensity sweetener, aspartame, may be associated with allergic/hypersensitivity–type reactions.*
**Methods:** *We conducted a multicenter, placebo-controlled clinical study to evaluate individuals who had experienced urticaria and/or angioedema allegedly associated with ingestion of an aspartame-containing product. Despite extensive recruiting efforts over 4 years, only 21 subjects could be enrolled. After admission to clinical research units, subjects were given aspartame and placebo in a randomized, double-blind, crossover fashion. Subjects received, on different days, increasing doses (50, 300, 600 mg) of aspartame and placebo at 8:00 AM, 10:00 AM, and noon. Subjects who weighed less than 40 kg received one half of these doses. Conversion products of aspartame, aspartylphenylalanine diketopiperazine and β-aspartame, were also included in the aspartame arm of the study. Positive reactions were defined as urticaria (hives with wheals 4 mm or more in diameter with a collective diameter of at least 15 mm or one or more hives with a wheal of 4 mm or greater with a flare of 8 mm or greater) or as angioedema.*
**Results:** *According to these criteria, four reactions were observed; two followed aspartame ingestion and two followed placebo ingestion ($p = 1.00$). The incidence of other adverse experiences was no different after aspartame versus placebo ingestion ($p = 0.289$).*
**Conclusion:** *These results indicate that aspartame and its conversion products are no more likely than placebo to cause urticaria and/or angioedema reactions in subjects with a history consistent with hypersensitivity to aspartame. (J ALLERGY CLIN IMMUNOL 1993;92:513-20.)*

***Key words:*** *Aspartame, food additive, double-blind challenges, hypersensitivity, allergy, clinical study*

Aspartame, the dipeptide L-aspartyl-L-phenylalanine methyl ester, is a widely used, high-intensity sweetener that is present in over 5000 products worldwide. There have been isolated reports that aspartame may cause allergic/hypersensitivity–type reactions.[1-3] Absorption of intact aspartame has been postulated to trigger these reactions. However, aspartame is not absorbed as an intact molecule; rather, it is metabolized in the gastrointestinal tract to three common dietary

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*Abbreviations used*
CDC: Centers for Disease Control
DKP: Diketopiperazine

components—aspartic acid, phenylalanine, and methanol.[4, 5]

Most accounts of allergic/hypersensitivity–type reactions thought to be related to aspartame have been anecdotal and difficult to substantiate. In 1984, the Food and Drug Administration asked the Centers for Disease Control (CDC) to evaluate reports of symptoms possibly caused by aspartame.[6, 7] Of the 517 complaints investigated, 76 (15%) were allergic or dermatologic in nature. Because most symptoms were subjective, mild in nature, and common in the general population, the CDC could not identify specific complaints directly attributable to aspartame. The CDC concluded that well-designed clinical studies in individuals allegedly sensitive to aspartame would be needed to distinguish between symptoms "due to the suggestibility of some persons" and an "as yet undefined sensitivity of some individuals to aspartame in commonly consumed amounts."[6] We designed a multicenter, randomized, double-blind, placebo-controlled, crossover clinical study to determine whether urticaria and/or angioedema could be attributable to aspartame. Our objectives were twofold: (1) to determine whether individuals who had experienced such reactions, allegedly after consumption of an aspartame-containing product, would demonstrate these reactions on challenge with aspartame compared with placebo and (2) to describe clinical parameters of such reactions that might occur. Conversion products of aspartame, aspartylphenylalanine diketopiperazine (DKP) and β-aspartame, which are present in aspartame-containing products (particularly those stored for long periods of time), were included to evaluate the possibility that allergic/hypersensitivity–type reactions could be caused by them, rather than by the parent compound.[8] The results indicate that aspartame and its conversion products are no more likely than placebo to cause urticaria and/or angioedema reactions in subjects with a history consistent with hypersensitivity to aspartame.

## METHODS

### Study sites

Six centers participated in the study. These were The Children's Hospital/Harvard Medical School, Boston; Northwestern Memorial Hospital/Northwestern University Medical School, Chicago; Ottawa Civic Hospital/University of Ottawa Medical School, Ottawa, Ontario, Canada; Center for Health Sciences, University of California Los Angeles School of Medicine, Los Angeles; Duke University Medical Center, Durham, N.C.; Barnes Hospital and St. Louis Children's Hospital/Washington University School of Medicine, St. Louis. The study protocol was approved by the respective institutional review boards.

### Recruitment of subjects

We proposed studying 120 subjects (20 at each of the six study sites) who had experienced urticaria and/or angioedema within 12 hours of consuming a product containing aspartame. Recruitment letters were mailed to 4700 allergists in the United States and Canada asking them to refer suitable patients. Advertisements were placed in the JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY and *Annals of Allergy*, and 11 local allergy and dermatology societies were contacted. In addition, 102 individuals who had filed complaints of urticaria and/or angioedema allegedly related to aspartame with The NutraSweet Company (Deerfield, Ill.) were contacted.

A toll-free, long-distance telephone number, publicized by letter and advertisements, was established at one of the study sites to prescreen potential study candidates. Those who satisfied study inclusion criteria were referred to the investigational center closest to their residence for a final participation decision by the physician investigator. Of 188 potential candidates contacted, 111 called the toll-free number. Of these, only 21 could be enrolled in the study. Two additional individuals were admitted to the study sites; however, one was excluded because of pregnancy and one because of dermatographism. Forty-four subjects did not meet study inclusion criteria, and 32 declined to participate. Nine were lost to follow-up after initial contact, and three others were able to consume aspartame with no problems. Because of the difficulty in enrolling suitable subjects, the study continued for 4 years.

### Inclusion and exclusion criteria

Inclusion criteria were a history of urticaria or angioedema within 12 hours of ingestion of an aspartame-containing product during the previous 3 years or a history of chronic urticaria, which resolved without medication on cessation of aspartame consumption and recurred when consumption was resumed, a positive histamine skin test result, age of 10 to 65 years, informed consent, and willingness to remain in a research center for the duration of the study. Exclusion criteria were homozygous phenylketonuria, confounding medication within 3 weeks before entry into study, concomitant illness or abnormal laboratory test results that might interfere with the study results, aspartame ingestion within 3 weeks of entry into the study, an episode of urticaria or angioedema in the 3 weeks before entry

into the study, pregnancy, and dermatographism. Employees and family members of employees of The NutraSweet Company were also excluded.

## Clinical and laboratory evaluations

Subjects were admitted to the clinical research facility at the study site for screening the day before the first study period. Medical history included a detailed questionnaire with special attention to the reported allergic/hypersensitivity–type reaction(s) to aspartame. A physical examination was performed. Routine hematologic tests (complete blood count with differential count); urinalysis (gross and microscopic); urine pregnancy test (women of childbearing potential only); and determinations of serum concentrations of total protein, albumin, calcium, inorganic phosphorus, cholesterol, glucose, urea nitrogen, uric acid, alkaline phosphatase, lactate dehydrogenase, total bilirubin, aspartic aminotransferase, alanine aminotransferase, sodium, potassium, chloride, carbon dioxide, and creatinine were done. A prick test with 1 mg/ml histamine was performed, and results were positive in all 21 subjects challenged.

## Challenge procedures

Eligible subjects signed an informed consent form and were enrolled in the 5-day study. They remained in the study center throughout the trial, unless a positive reaction occurred in the first arm of the challenge, and were identified by a letter representing the specific site (A to F) followed by a two-digit number. A randomized protocol schedule for each site was generated independently by an academic statistician, who was not otherwise directly involved in the study. All study personnel (including statisticians, clinical monitors, study site personnel, and data-base management personnel) remained blind to treatment sequences until the data base was complete.

The 5-day study consisted of: day 1, admission and physical and laboratory workup; day 2, ingestion of test material (arm 1); day 3, washout; day 4, ingestion of test material (arm 2); day 5, follow-up and discharge. Subjects ingested aspartame and placebo in random sequence. Subjects were free to walk around the clinical research units but were not permitted to go where food or beverages were available. Meals were standardized on both treatment days, and no aspartame-containing products were included. Breakfast was served at 9:00 AM and lunch at 1:00 PM. Hot drinks were included with both meals. A dietitian kept a dietary documentation worksheet to record all food consumed on test days.

Test articles consisted of capsules containing 25 mg or 300 mg aspartame, capsules containing 7.5 mg DKP and 3.75 mg β-aspartame with 13.75 mg microcrystalline cellulose, and identical placebo capsules containing 25 mg or 300 mg microcrystalline cellulose (Avicel PH 102, FMC Corp., Newark, Del.). At the end of the study, the contents of the capsules (aspartame, DKP, β-aspartame, and placebo) for all subjects were verified according to the randomization schedule by an independent laboratory. The aspartame used in the study also contained approximately 0.32% DKP and 0.35% β-aspartame. In order to mask any residual sweetness from aspartame on the capsule and assure maintenance of the blind, subjects swished and expelled orange juice just before dosage. Subjects who weighed 40 kg or more received a total dose of 950 mg of aspartame administered at 8:00 AM (50 mg), 10:00 AM (300 mg), and noon (600 mg) and 7.5 mg β-aspartame + 15 mg DKP given together with the last dose of aspartame. Subjects who weighed less than 40 kg received one half of these amounts. The schedule for placebo was identical to that for aspartame. All capsules were given with 2 to 4 ounces of water.

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) were determined immediately before ingestion of test material, 15 minutes afterward, and at 2:00 PM, 4:00 PM and 8:00 PM on challenge days. Subjects were monitored at all times for possible urticaria or angioedema and any other adverse experiences. The nature, onset, duration, severity, and resolution of all adverse experiences were recorded for all events.

Positive responses were defined as the occurrence of urticaria or angioedema. Criteria for urticaria were hives with wheals of 4 mm or more in diameter with a collective diameter of at least 15 mm or one or more hives with a wheal of 4 mm or more in a diameter with a flare of 8 mm or greater. The number, size, and location of the hives were recorded. The location of any angioedema was recorded. Angioedema consisting of laryngeal stridor was to be diagnosed by a qualified observer using indirect laryngoscopy. All reactions were documented by photographs. If responses were mild, subjects were not to receive medication but were to be observed for 24 hours and then discharged. Subjects with severe reactions were to stop the test material and receive appropriate medical treatment. If the reactions occurred during the first study arm, the subject was to wait at least 2 weeks before reentering the study to complete the crossover arm. All reactions were to be followed up and treated until they resolved.

## Statistical analysis

A two-tailed McNemar's test at the 5% significance level in its exact form[9] was used to determine the significance of the incidence rates of adverse events after ingestion of aspartame and placebo. Our initial plan to enroll 120 subjects was designed to detect a 12% difference in incidence of urticaria and/or angioedema between aspartame and placebo with 80% probability. Miettinen's method for the power of the matched pairs test for equality of proportion[10] was used, assuming an incidence rate of 10% after ingestion of placebo. After 3 years of recruitment efforts, we evaluated the statistical impact of stopping the study with a smaller number of subjects and made a decision

**TABLE I.** Characteristics of study subjects and complaints anecdotally attributed to aspartame

| Subject No.* | Age (yr) | Sex | Race/ethnicity | Complaints |
|---|---|---|---|---|
| A01 | 31 | F | Caucasian | Urticaria, angioedema |
| A02 | 54 | F | Caucasian | Urticaria, angioedema, chronic urticaria |
| B01 | 23 | F | Caucasian | Urticaria |
| B02 | 42 | F | Caucasian | Urticaria, angioedema, difficulty breathing, chest pain, weakness |
| B03 | 10 | M | Caucasian | Urticaria, angioedema, respiratory difficulty |
| C01 | 34 | F | Caucasian | Urticaria, abdominal discomfort, asthma, rhinitis, nausea, diarrhea, vomiting |
| C03 | 50 | F | Caucasian | Urticaria, angioedema |
| D01 | 42 | F | Caucasian | Urticaria, angioedema, chronic urticaria, joint pains, mental confusion, swollen tongue |
| D02 | 25 | F | Hispanic | Urticaria, angioedema |
| E01 | 42 | F | Caucasian | Urticaria, angioedema; scratchy, swollen throat |
| E02 | 40 | F | Caucasian | Urticaria |
| E03 | 29 | M | Caucasian | Urticaria, lacrimation, rhinorrhea, sneezing, chest tightness, shortness of breath |
| E04 | 27 | F | Hispanic | Urticaria, angioedema |
| E05 | 39 | F | Caucasian | Urticaria, headache |
| E06 | 21 | F | Caucasian | Urticaria |
| F01 | 29 | F | Caucasian | Urticaria |
| F02 | 24 | F | Caucasian | Angioedema |
| F03 | 26 | F | Caucasian | Urticaria, depression, "PMS-like syndrome" |
| F04 | 45 | M | Caucasian | Urticaria, angioedema |
| F05 | 16 | F | Caucasian | Urticaria |
| F06 | 55 | M | Caucasian | Urticaria, loose stools, pruritus |

*The six clinics are represented by the letters A to F. *A*, Duke University Medical Center; *B*, The Children's Hospital/Harvard Medical School; *C*, Northwestern Memorial Hospital/Northwestern University; *D*, Barnes Hospital and St. Louis Children's Hospital/Washington University; *E*, University of California Los Angeles School of Medicine; *F*, Ottawa Civic Hospital/University of Ottawa Medical School.

to end the study once 20 to 24 suitable subjects had been evaluated. The study was stopped after 21 subjects completed both arms. This number of subjects is adequate to detect a 39% increase in urticaria and/or angioedema from aspartame relative to placebo with the 10% placebo incidence rate. On the basis of this analysis, we came to the conclusion that this is a reasonable detectable difference when one considers the expectation that 100% of the subjects had been identified as having had urticaria and/or angioedema thought to be associated with aspartame. Thus 21 subjects would be sufficient to discriminate between aspartame and placebo in a population identified as alleged responders.

## RESULTS

### Subject characteristics

Twenty-three subjects were screened at the study sites. Two of them were disqualified from participation in the study; one had a positive urine pregnancy test result and the other had

**TABLE II.** History of allergic/hypersensitivity–type reactions allegedly related to aspartame

| | Number of subjects ($n$ = 21) |
|---|---|
| Reaction required medical attention | 15 |
| Reaction required treatment with drugs | 12 |
| Disappeared on discontinuation of aspartame-containing products | 20 |
| Recurred on rechallenge with aspartame-containing products | 20 |
| Associated with more than one aspartame-containing product | 17 |
| Same reaction every time an aspartame-containing product was consumed | 18 |

**TABLE III.** Positive reactions that occurred during the study

| | Nature of reaction | | | | | |
|---|---|---|---|---|---|---|
| Subjects | No. of Hives | Wheal (mm) | Flare (mm) | Time of onset* | Duration | Challenge |
| B01 | 1† | <4 | – | 13 hr/45 min | 45 min | Aspartame |
| | 1 | 40 | 65 × 140 | 14 hr/45 min | 9 hr/45 min | |
| | ..... | ..... | ..... | ..... | ..... | ..... |
| | 1 | 40 | 85 | 31 hr/15 min | 2 hr/15 min | Washout |
| F03 | 1† | 1.5 | 10 × 8 | 4 hr/10 min | 30 min | Aspartame |
| | 1 | 4 × 4 | 15 × 15 | 7 hr/55 min | 30 min | |
| | 1† | 2 | 5 | 10 hr/55 min | 1 hr | |
| E04 | Generalized | 50 (largest hive) | 150 | 1 hr | 4 mo | Placebo |
| F05 | 1 | 4 | 32 | 2 hr/30 min | 1 hr/25 min | Placebo |

*Relative to first dose.
†Hive did not meet study criteria for a positive reaction.

dermatographism as determined by physical examination. Twenty-one subjects satisfied the enrollment criteria, and all of them completed both arms of the study. Two sites studied six subjects each, and the other four sites studied two to three subjects each. There were sporadic, mild, "out of normal range" laboratory values in some subjects before study participation. However, we did not believe that any of these findings would interfere with the results of the study.

The characteristics of the 21 study subjects are shown in Table I. Seventeen subjects were female, and four were male. There were 19 white subjects and two Hispanic subjects. Age ranged from 10 to 55 years (mean, 34 ± 12 years), and two subjects were under the age of 21. The mean height was 163.16 ± 8.86 cm, and the mean body weight was 70.38 ± 17.72 kg. Historically, of the 21 subjects who completed the study, 10 had experienced urticaria only, 10 had experienced both urticaria and angioedema, and one had experienced angioedema. All episodes of angioedema and/or urticaria occurred within minutes up to 8 to 10 hours after consumption of products containing aspartame. Generally, the subjects reported that the urticaria involved many areas of the body, and most of the subjects complained of several episodes of these symptoms. Nine individuals also experienced other accompanying symptoms including respiratory difficulty, gastrointestinal symptoms, rhinitis, and headache. Approximately one third of the subjects also reported having experienced urticaria and/or angioedema after ingestion of other foods (five) or drugs (three); seven subjects reported histories of asthma and/or allergic rhinitis.

Table II shows the characteristics of the allergic/hypersensitivity–type reactions historically reported in association with ingestion of aspartame. In 15 of the 21 subjects, these reactions required medical attention. Twelve of the subjects had reactions of sufficient severity to warrant treatment with drugs; six were treated with epinephrine and/or steroids, and 10 were treated with antihistamines. Twenty of the subjects reported that their symptoms disappeared when they discontinued use of products containing aspartame, and 20 subjects reported recurrence on rechallenge. Seventeen of the subjects associated their reactions with more than one product containing

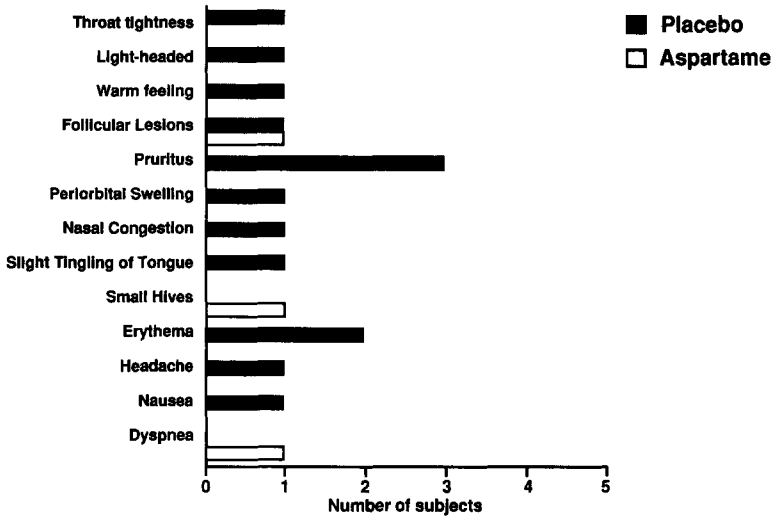


**FIG. 1.** Other adverse experiences that occurred on challenge days.

aspartame. Eighteen subjects reported the same reaction every time they consumed a product with aspartame.

### Incidence of reactions after challenge

Seventeen of the 21 subjects had no positive reactions during the study, whereas four subjects exhibited urticaria that met the study criteria. Two of these four subjects (F03 and B01) had urticaria after ingestion of aspartame but not placebo; the two others (E04 and F05) had urticaria after ingestion of placebo but not aspartame. All four reactions occurred during the first arm of the study. There was no statistically significant difference in the incidence of positive reactions ($p = 1.000$) between aspartame and placebo challenges.

Table III details the reactions observed in the four subjects. All reactions on challenge days consisted of urticaria, which occurred from 1 hour to almost 15 hours after ingestion of the test substance. Reactions lasted from 30 minutes to 4 months. The two subjects with positive reactions after aspartame ingestion experienced only one hive each on the days of the challenge, which met the study criteria for a positive reaction and one to two smaller hives, which did not meet the study criteria. One of these two subjects (B01) also had a hive during the washout day. Of the two subjects with positive reactions after placebo ingestion, one (F05) had a single hive on the day of the challenge, which met the study criteria, whereas the other individual (E04) experienced generalized urticaria, which persisted for 4 months and required treatment with $H_1$- and $H_2$-histamine blockers and orally administered corticosteroids.

Ten subjects experienced a total of 17 other adverse events. These are detailed in Fig. 1. Two had adverse experiences after ingestion of aspartame but not placebo, and six had adverse experiences after ingestion of placebo but not aspartame. There was no statistically significant differences ($p = 0.289$) between aspartame and placebo challenges in the number of subjects with adverse experiences. In addition, one subject who had follicular lesions at the time of admission to the study had an additional follicular lesion during the washout period that followed 32 hours after placebo challenge. All adverse events were mild in nature.

Adverse experiences after placebo were pruritus (B02, E03, E06), erythema (E03, E06), lightheadedness (A01), throat tightness (A01), warm feeling (A01), nasal congestion (B02), periorbital swelling (B02), tingly tongue (C03), headache (E03), and nausea (E04). Adverse experiences after aspartame ingestion were two small hives, which did not meet study criteria (D01), and dyspnea, with normal spirometric studies (F02). One subject (A02) had the same adverse experience (follicular lesions) after both aspartame and placebo challenges.

Vital signs taken at the time points specified in the protocol (Methods) remained stable throughout, showing little variation. No clinically significant changes were noted.

## DISCUSSION

The present study was performed in the setting of clinical research centers because we believed that it would ensure maintenance of the double-blind format, uniformity of the diet during both aspartame and placebo challenges, and appropriate administration of the test articles. The results obtained in this rigorous multicenter, randomized, double-blind, placebo-controlled, crossover clinical study indicate that aspartame and its conversion products (DKP and β-aspartame) were no more likely to cause urticaria and/or angioedema or other adverse experiences than an inert placebo.

An important finding of our study was the difficulty we experienced in identifying individuals who gave a history of association between aspartame ingestion and symptoms suggestive of allergic/hypertensive–type reactions, specifically urticaria and/or angioedema. Extensive recruiting efforts over 4 years in both the United States and Canada yielded only 86 referrals, in addition to the 102 subjects who had previously registered complaints with The NutraSweet Company. This strongly suggested that if allergic/hypersensitivity–type reactions to aspartame do exist, the incidence is rare.

Of the 111 subjects that we were able to prescreen, only 21 could be enrolled in the study. According to the criteria of the CDC for determining the likelihood of an association between aspartame and an anecdotal report of an adverse effect,[7] all of the 21 subjects enrolled had a high potential for having allergic/hypersensitivity–type reactions to aspartame. All subjects had experienced urticaria and/or angioedema within minutes to hours after consumption of a product with aspartame. Most of the subjects complained of several such episodes. Twenty of the 21 subjects reported that their symptoms resolved with discontinuation of aspartame-containing products, and 20 of the 21 reported recurrence of the symptoms on rechallenge. Seventeen of the 21 subjects reported reactions with more than one aspartame-containing product (Table II). Furthermore, 12 of the 21 subjects reported reactions of sufficient severity to warrant treatment with drugs. In light of these observations, our failure to document any difference in the incidence of urticaria and/or angioedema or other adverse experiences after aspartame challenge versus placebo challenge is all the more striking.

The doses used in this study are equivalent to the amounts in approximately 1 to 2 L of degraded beverage. Because the dose of aspartame is approximately five to six times the average amount of aspartame currently being consumed (90th percentile),[11] our failure to document allergic/hypersensitivity–type reactions to aspartame or its conversion products is unlikely to have been due to limitations in the challenge doses used.

The results of this study are in agreement with those reported previously by Garriga et al.,[12] who experienced similar difficulty in finding appropriate subjects to study. They were able to evaluate only 12 subjects during a 32-month recruitment period. No reproducible reactions to aspartame were found.

In summary, we could not document a relationship between aspartame and urticaria and/or angioedema or any other adverse experiences in a population of subjects with a history that was highly suggestive of an association between aspartame ingestion and the occurrence of allergic/hypersensitivity–type reactions. Thus physicians with patients who believe that aspartame may have caused an allergic/hypersensitivity–type reaction should carefully evaluate other possible causes.

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# Comparison of azelastine and chlorpheniramine in the treatment of mastocytosis

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**Background:** *Azelastine, a novel antiallergic medication, was compared with chlorpheniramine maleate for efficacy and safety in the treatment of systemic mastocytosis.*
**Methods:** *Fifteen subjects with mastocytosis participated in a double-blind, randomized, three-period, crossover trial, which compared an azelastine regimen of 4 mg or 8 mg every 12 hours with a chlorpheniramine regimen of 12 mg every 12 hours. Response to therapy was assessed by daily symptom scores, extinction dilution skin tests, plasma histamine levels, and global evaluations.*
**Results:** *Subjects' mean wheal area responses provoked by histamine or morphine sulfate were significantly lowered by azelastine when compared with chlorpheniramine. Plasma histamine levels in subjects receiving azelastine or chlorpheniramine were not significantly different. There were no significant differences between azelastine and chlorpheniramine in individual symptom scores or global evaluations except that azelastine at both doses significantly relieved pruritus and at 4 mg significantly relieved abdominal pain and that chlorpheniramine was associated with less fatigue in comparison to azelastine at 8 mg.*
**Conclusions:** *It thus appears that azelastine is superior to chlorpheniramine in suppressing skin responses to histamine and morphine sulfate and in suppressing pruritus in patients with mastocytosis. However, when all parameters are considered, neither drug is clearly superior for the treatment of patients with mastocytosis. (J ALLERGY CLIN IMMUNOL 1993;92:520-6.)*

***Key words:*** *Mastocytosis, antihistamines, mast cells, histamine, clinical trial*

Mastocytosis is a disease of unknown etiology characterized by the presence of excessive numbers of mast cells in the skin and internal organs such as the bone marrow, gastrointestinal tract, liver, and spleen.[1] Subjects with this disorder frequently have manifestations related to the presence of excess mast cells and release of mast cell–derived mediators. The most common signs and symptoms include pruritus, flushing, urticaria, bone pain, abdominal pain, diarrhea, and occasionally malabsorption. Treatment of this disease is directed at controlling the mast cell mediator–induced signs and symptoms by either stabilizing the mast cell membrane (with cromolyn sodium) or blocking the effects of histamine with $H_1$ and $H_2$ histamine antagonists (e.g., chlorpheniramine

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