

Correspondence

Aspartame-induced hives

To the Editor:

The failure by Geha et al. (*J ALLERGY CLIN IMMUNOL* 1993;92:513-20) to find more than two subjects with aspartame-induced hives may have resulted from flaws in study design. After reviewing their study protocol in 1986 to 1987, I declined to take part because I identified the defects numbered below.

My perspective is based on my own additional experience with aspartame-induced hives, summarized as follows.

During 1986, after reporting two index cases,¹ I was contacted by 88 individuals in the St. Louis area who had heard a direct televised appeal for subjects and had suspected that their chronic urticaria or angioedema might be due to aspartame. By contrast, indirect attempts to recruit subjects (i.e., appeals to local allergists) yielded no referrals during the same period. Few of my telephone respondents had consulted an allergist.

Seventy-five of the individuals who telephoned were willing to avoid aspartame for 2 weeks; 50 experienced complete resolution of hives upon aspartame avoidance; 22 were willing to openly rechallenge themselves with aspartame, and each re-experienced allergic skin reactions. With resources to study only six of these individuals, I found four of them (all women) who experienced hives after double-blind, placebo-controlled challenges with aspartame. One subject (age 40) had a reaction 3 hours after challenge, which was similar to the initial cases¹; one subject (age 26) had an immediate reaction and a delayed reaction 12 hours after challenge; one subject (age 29) had an "immediate" reaction 2.5 hours after challenge and subsequent delayed outbreaks of hives at 9, 23, 30, and 43 hours, which required treatment; and one subject (age 43) had only a delayed reaction at 22 hours after challenge; no subjects reacted to placebo. Thus it should not be surprising that the subjects B01 and F03 in the study by Geha et al. experienced delayed reactions to aspartame. Allergists need to recognize that aspartame-induced hives can be acute, delayed, or chronic.

The defects I identified in the study by Geha et al. are the following:

1. *Subject recruitment methods.* There are two types of recruiting: direct appeals to subjects and indirect appeals through physicians. Indirect recruiting is less successful when subjects rarely visit physicians and when physicians are not actively looking for a given disorder. Geha et al. relied primarily on indirect types of recruiting and garnered only 86 referrals. I found that direct appeals to patients via television were essential for adequate recruitment of aspartame-allergic subjects. From my perspective, the recruiting efforts of Geha et al. were inadequate to address the problem of aspartame-induced hives, and therefore their conclusion that "the

incidence (of aspartame-induced urticaria) is rare" is unwarranted. There remains no study that adequately defines the incidence of aspartame-induced hives in the population.

2. *Convenience, compensation, and safety for subjects.* Geha et al. note that 32 of the individuals contacted "declined to participate." Their study design probably tended to discourage the participation of the subjects who were likely to be allergic to aspartame. Why? The more a potential subject finds that aspartame consumption correlates with hives, the less motivation the potential subject has to learn about the cause of his or her hives and to participate in an inconvenient, 5-day hospital stay, especially if compensation is inadequate. The more uncertain the correlation, the more likely a potential subject might be to welcome an extensive evaluation. (The authors should disclose the financial compensation to subjects; it may have been inadequate to encourage sufficient subject participation.) Also, subjects with more severe or delayed symptoms would be more likely to decline to participate because of the potential for a severe reaction. Having once experienced that one diet soda could produce severe or delayed allergic reactions, some of the potential subjects most sensitive to aspartame may have been unwilling to participate out of concern for their safety. (The study required ingestion of the equivalent of over six cans of diet soda.) Obviously, the nine enrolled subjects in the study by Geha et al. who had required no medications did not have severe urticaria or angioedema.

My challenge procedures were more conveniently designed. They involved two 4-hour outpatient visits, usually on Saturdays, with 50 mg of aspartame. The six subjects that I found to have positive responses to double-blind, placebo-controlled challenges to aspartame were unwilling to be referred to the Geha et al. study because they believed it would be too inconvenient and possibly unsafe.

Thus several aspects of the Geha et al. study design may have contributed to selectively discourage the participation of the subjects likely to be allergic to aspartame.

3. *Inclusion or exclusion criteria and challenge design.* Avoiding "confounding (but unspecified) medication within three weeks" is not adequate preparation for aspartame challenges. The national task force recommendation to avoid astemizole for at least 6 weeks, and also tricyclic antidepressants, before skin testing² should clearly apply to this type of challenge study. Because astemizole, which can suppress responses to skin tests (and presumably challenges) for possibly up to 12 weeks, has been commonly used in treatment of chronic urticaria, prior astemizole use might explain some of the negative aspartame challenge results. Withdrawal from astemizole might account for one or both of the "posi-

tive" placebo challenge results. I ask the authors, "How many subjects had taken astemizole during the 12 weeks before their challenges?" (Also, what justifies the authors' apparent assumption that "a positive histamine skin test" will guarantee a positive challenge?)

Although five subjects in the "population identified as alleged responders" by Geha et al. had food-induced hives and seven subjects had allergic respiratory problems, apparently no effort was made to limit the subjects' diets or to exclude other recognized causes of chronic urticaria.³

Because of these deficiencies in study design, I am concerned that the NutraSweet Company-sponsored study by Geha et al. does not accurately reflect the incidence of aspartame-induced hives. I hope that, from among the dozens of allergists who have cases of aspartame-induced hives, additional studies will be forthcoming.

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The contribution of the side chain of penicillins in the induction of allergic reactions

To the Editor:

I thank Dr. Blanca for his interest in our article "The frequency of skin test reactions to side chain penicillin determinants" (*J ALLERGY CLIN IMMUNOL* 1993;91:694-701). As the title indicates, we have shown that side-chain-specific immediate skin test reactions to semisynthetic penicillins can be demonstrated in patients in whom a presumed allergic reaction to a semisynthetic penicillin has clinically developed. Unfortunately, we have not yet shown that patients who have immediate skin test reactivity only to side-chain determinants (1) react clinically when challenged with that penicillin and (2) tolerate penicillins lacking that side-chain determi-

nant. Nevertheless, it would appear that the side-chain specificity demonstrated in our study does have some clinical significance, because although side-chain-specific skin test reactions occurred in 12.8% of 78 patients who clinically reacted to a semisynthetic penicillin, no side-chain-specific skin test reactions occurred in 34 patients whose clinical allergy was to penicillin itself. This difference was significant ($p < 0.0005$). So the previous occurrence of a semisynthetic penicillin-induced reaction was associated with the skin test reactivity to side-chain determinants, but such reactivity did not occur when penicillin itself was the precipitant of a clinical reaction.

It is important to point out that there was an increased proportion of exanthemata not usually associated with IgE-mediated reactivity in the patient group with side-chain-specific reactions, which raises a question as to whether the skin test reactivity has clinical significance in all the individuals tested.

Regarding the discrimination between ampicillin and amoxicillin in IgE-mediated allergic reactions, this question is still unanswered. Our investigations of T-cell-mediated reactivity in patients with ampicillin-induced rash indicate that their T cells cannot distinguish between the two determinants, in support of Dr. Blanca's findings.¹ But B cells may be capable of making this distinction.

There are two important questions that remain to be answered. First, are we missing patients with clinically significant immediate hypersensitivity to semisynthetic penicillins if we skin test only with benzylpenicillin derivatives, and therefore should semisynthetic penicillins be added to the battery of skin test reagents that we use? Second, can we conclude from the presence of side-chain-specific skin test reactivity that we can safely administer a β -lactam lacking that side-chain determinant to a patient requiring antibiotic therapy? Dr. Blanca's findings suggest that the answers to these questions may be sometimes in the affirmative, but more study is needed before definitive conclusions can be reached.

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