

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

To the Editor:

In the article, "The frequency of skin test reactions to side chain penicillin determinants" (J ALLERGY CLIN IMMUNOL 1993;91:694-701), Sylviu-Dan et al. demonstrate the relevance of side chain-derived penicillin structures for the diagnosis of allergic reactions to β -lactams. As mentioned by Adkinson,¹ the contribution of side chain-derived reagents of different penicillins should be determined by different investigators in different populations. This study is an example, and other studies have now appeared.² We would like to add some data and comment on some differences between the work of Sylviu-Dan et al. and the results of other authors.^{2,3} In the series reported by Sylviu-Dan et al. the most common reaction-inducing drug was amoxicillin, in 33% of the cases, followed by benzylpenicillin in 30% and ampicillin in 24%. In our series⁴ amoxicillin was involved in 50% of the cases, benzylpenicillin in 28%, and ampicillin in 9.8%. In a recent study carried out by Audicana et al.² the involvement of amoxicillin was 58%, ampicillin 20%, and benzylpenicillin 18%. The other penicillin derivatives involved in all of these studies, such as cloxacillin or metampicillin, contributed with a lower percentage. In order to compare the results between different countries, it is important to provide information about the involvement of amoxicillin, ampicillin, and benzylpenicillin in the induction of the reactions in these patients. However, since in many cases the data concerning drug involvement are taken retrospectively on the basis of the clinical history, when subjects refer to having taken amoxicillin, ampicillin, or cloxacillin they are usually correct because they give the specific name, but when they refer to having taken penicillin it cannot be assumed that it was benzylpenicillin. This is a problem that occurs in our studies and may well happen to other authors. This implies that in a certain percentage of cases the specific penicillin cannot be stated, which means that the contribution of benzylpenicillin in the total group is in fact lower than reported.^{2,4}

Although the consumption of amoxicillin and ampicillin in the groups studied was over 50%, the contribution of skin testing with the native drug or minor determinant mixture of amoxicillin and ampicillin was below 50%: 47% in the study of Sylviu-Dan et al., 26% in the results of Audicana et al.,² and 22% in the results of Blanca et al.³ This implies that in many instances subjects have cross-reactivity between the different penicillins because the reaction was induced by ampicillin or amoxicillin and they had positive skin test responses to major and minor determinants of benzylpenicillin. However, in these studies there are differences in the percentage of positive response to ampi-

cillin and amoxicillin, although in all of the studies the drug most frequently taken was amoxicillin.

In one study⁴ when skin test responses to ampicillin were positive, responses were also positive to either amoxicillin or benzylpenicillin, and in no case did ampicillin alone contribute to induction of a positive response. In another study in two cases ampicillin produced a positive response with negative skin test response to amoxicillin,² and in the work of Sylviu-Dan et al. the skin test response was positive to ampicillin in eight cases and to amoxicillin in one, although in this study amoxicillin was not skin tested in all cases (as the authors mention in their work), so no definitive conclusion can be drawn concerning the positivity to both happens in this study group. These results raise important questions as to the ability of ampicillin to induce selective responses with good tolerance to amoxicillin. To our knowledge, no selective reactions to this compound with good tolerance to benzylpenicillin and amoxicillin have been reported. Additional results from *in vitro* studies support the same *in vivo* findings.⁴ However, the production of hybridomas has shown that there can be monoclonal antibodies that recognize mainly the side chain of either amoxicillin or ampicillin with little cross-reactivity, which indicates that there are differences in both structures.^{5,6}

In order to add more support to the role of the side chain structure in inducing selective reactions to semi-synthetic penicillins, we have studied a group of 32 non-IgE-mediated exanthematous and/or urticarial reactions induced by penicillins.⁷ Over 40% of subjects had a positive delayed skin response to amoxicillin and ampicillin, and only 10% had such a response to benzylpenicillin, though all of these subjects also had positive response to amoxicillin and ampicillin. After challenging 29 of the 32 subjects from this group, two responded to penicillin V, and the rest were selective reactors to either amoxicillin or ampicillin with good tolerance to benzylpenicillin and penicillin V. All of these data indicate the relevance of amoxicillin and ampicillin in the study of allergic reactions to penicillins. Since amoxicillin is one of the most commonly prescribed drugs, followed by penicillin V and ampicillin, in the countries where these studies were carried out,⁸ cases with reactivity to determinants generated by amoxicillin and ampicillin can reasonably be expected to be found. Accordingly, a similar approach should therefore be taken to establish the contribution to positivity of the different penicillins and the relationship with the consumption of drugs by the population in which these studies are carried out. These studies will greatly benefit those patients who are allergic to penicillins.

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1/8/56075

Intentional diagnostic sting challenges: an important medical issue

To the Editor:

In a letter in the May 1993 issue of the JOURNAL, Robert E. Reisman (page 1100) expresses his concern about three aspects of our study in which deliberate sting challenges were performed (*J ALLERGY CLIN IMMUNOL* 1992;90:110-8). First is the potential danger of inducing an anaphylactic reaction in otherwise healthy subjects. In the referred study by Smith et al. and in the original study on which this article was based,¹ no clinical data on any of the 59 insect-sting-challenged subjects were given. In three patients anaphylactic shock developed, but we were not informed about the use of β -blockers or concurrent atherosclerotic, pulmonary, or other diseases in these patients, which might have influenced the clinical reaction after the sting. In our study, subjects were selected carefully to minimize potential risks due to sting challenges. In addition, all challenges were carried out in an intensive care unit. When a severe anaphylactic reaction occurred (17 of 138 subjects), these persons stayed overnight for observation. As indicated, none of them required any additional therapy. There was thus no medical indication,

other than a need for reassurance, for keeping these subjects hospitalized.

The second concern of Dr. Reisman deals with the identification of subjects at risk of developing another insect-sting anaphylactic reaction. Fortunately, insect-sting anaphylaxis is a self-limiting disease in most persons.² We agree with Dr. Reisman that the severity of the previous reaction relates to some degree to the reaction after a future sting. However, in our view this is not a sufficient criterion for starting immunotherapy. In a recent article (*J ALLERGY CLIN IMMUNOL* 1994;94: 151-9), we describe 324 subjects with previous insect-sting anaphylaxis. Of these subjects, 48% of the honey-bee-sensitive persons and 75% of the yellow jacket-sensitive persons did not react at all to a sting challenge. Of the patients with a previous severe reaction, only 30% of honeybee-sensitive persons and 15% of yellow jacket-sensitive persons had a severe reaction after this sting challenge. Upgrading from mild to severe reactions was never observed. In addition, none of the tests to assess insect-sting hypersensitivity (i.e., skin test, IgE, IgG₄) significantly related to the reaction after sting challenge, as demonstrated previously.³ Alarmingly, approximately 5% of subjects with negative skin test results or undetectable plasma levels of specific IgE did have a second anaphylactic reaction after sting challenge. These patients would normally not have been treated with venom immunotherapy, but they were at risk for a severe anaphylactic reaction after a future field sting. However, we prospectively demonstrate that subjects with a mild reaction after a field sting may not need to be treated with immunotherapy at all, and in this respect we agree with Dr. Reisman.

The real concern of our sting-challenge procedure was the reaction after future field stings. Preliminary results from questionnaires sent to all our (untreated) subjects with a negative sting-challenge test result show approximately 4% recurrence of (mild) anaphylactic symptoms after a field sting up to 10 years after the challenge. This rate is comparable to the prevalence of insect-sting anaphylaxis in the general population.² This indicates a benefit of relieving approximately 80% of subjects from unnecessary, costly, and time-consuming immunotherapy versus a 4% risk for a mild anaphylactic reaction in untreated subjects. Although we are well aware of the potential legal consequences regarding the sting-challenge procedure in the United States, we think that this risk-to-benefit ratio is low enough to advocate the standardized, in-hospital procedure as the best selection criterion for venom immunotherapy.

The third concern of Dr. Reisman is that we did not use epinephrine for treatment of all anaphylactic reactions in the intensive care unit. There are no prospective clinical trials on the use of epinephrine or any other medication in the treatment of anaphylaxis. We know that the therapeutic regimen in an intensive care