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News and commentaries

Importance of skin testing with major and minor determinants of benzylpenicillin in the diagnosis of allergy to betalactams. Statement from the European Network for Drug Allergy concerning AllergoPen withdrawal

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*The additional members of ENDA and European Academy of Allergology and the Clinical Immunology (EAACI) are given in the Appendix.

Key words: allergy; betalactams; determinants; diagnosis; skin tests.

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Allergy to betalactams is the most frequent cause of allergic drug reactions. Reliable *in vivo* tests are available to diagnose IgE-mediated reactions (1, 2). *In vitro* methods are a less sensitive diagnostic alternative that cannot replace skin tests (2). From the outset, the importance of skin testing was emphasized by using benzylpenicillin conjugated to poly-L-lysine (PPL) and benzylpenicillin plus benzylpenicilloic acid, the so-called minor determinants (MDM) (2, 3). The production of betalactams with different chemical structures has increased, inducing allergic reactions with different IgE specificities; cross-reacting or selective (4). In the former, skin testing with PPL and MDM suffices for diagnosis, but in the latter, skin testing with the culprit drug is often required. Withdrawal from the market of PPL and MDM by AllergoPharma will severely hamper the diagnosis of allergy to betalactams. Alternative antibiotics may be more expensive or more toxic (2).

In addition to PPL and MDM, the European Network for Drug Allergy (ENDA) recommends the use of amoxicillin and in some instances the culprit betalactam (2), although PPL and MDM remain essential to identify skin-test-positive patients. In the allergological workup, the first step which could be recommended (1, 2) is to use PPL and MDM and, if negative, to undertake a drug-provocation test with benzylpenicillin. If this is negative, skin testing with amoxicillin and possibly with other betalactams, is necessary to complete the diagnosis. Thus, after following these steps in this order, cross-reacting or selective responders are separated. An alternative work up is to perform all skin tests in parallel and a drug provocation test with the culprit drug if they are all negative (2). In most instances, whatever betalactam involved, the use of PPL and MDM in the event of positivity also indicates that cross-reactivity exists (4).

The relevance of PPL and MDM was recently emphasized by Bousquet et al. (5) and Atanaskovic-Markovic et al. (6), who showed that these determinants induce a positive response in 46.7% and 85% of cases respectively. This percentage of positive responses may vary, not only in different populations but also over the years. In a study published in the 1990s, we saw that PPL and/or MDM represented 77.7% of total skin test positivity (4), whereas this figure was 42.1% in 2000 (1) and recent data from our files suggest it is currently 22.1% in 2005. These data clearly indicate that skin testing with PPL and MDM is necessary to evaluate patients allergic to betalactams. If we rely solely on clinical history, a higher percentage of cases will be falsely labelled as allergic. In USA these figures are even higher and it has been shown that of patients with allergic reactions to penicillin confirmed by skin test, 75% were positive to PPL, 10% to MDM, and 14.8% to PPL and MDM (7).

In Spain, major and minor determinants have been approved by national health authorities as allergens for skin testing, but differences in national regulations may not permit the use of these reagents everywhere. Preliminary comparisons show that the preparations apparently are comparable, although no statistical analysis has been performed yet. Thus, more precision is needed concerning their predictive values. We suggest that clinicians or researchers having problems obtaining these reagents access the ENDA web page for further details (http://www.eaaci.net). In summary, the following measures are recommended:

1 Use an equivalent kit for skin testing (Diater laboratories, Madrid, Spain) consisting of PPL and MDM (Sodium Benzylpenicillin, Benzylpenicilloic acid and benzylpenicilloate) in a research programme approved by an ethical committee until this product or an equivalent is approved in your country. As ENDA does not promote an un-validated reagent, we consider that a published validation is urgently needed.
2 Otherwise, use benzylpenicillin, amoxicillin, ampicillin plus the culprit betalactam, if this can be identified.

Although having a much lower sensitivity, *in vitro* testing has proved useful for diagnosis. The two methods available are the *in vitro* quantitation of IgE antibodies by immunoassay and the basophil activation test quantitated by flow cytometry. Because only a few studies exist, the literature should be consulted for information regarding the sensitivity and specificity of these assays.

Finally, we do not recommend to desensitize patients (as the American Academy of Allergy Asthma and Immunology [AAAA & I] recommends). In our experience patients can be correctly diagnosed and alternative betalactams found.

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Appendix

European Network for Drug Allergy (ENDA) and the EAACI interest group on drug hypersensitivity with the following additional members.

Drs W. Aberer, B.K. Ballmer-Weber, A. Barbaud, B. Bilo, A. Bircher, J. Birnbaum, B. Blömecke, P. Bonadonna, K. Brockow, P. Campi, Ch. Christiansen, O. Clement, P. Demoly, P. Dewachter, A. DeWeck, M. Drouet, G. Du Toit, C. Dzviga, B. Eberlein-König, H. Falpau, J. Fernandez, T. Fuchs, P. Gamboa, M. Gotua, J.L. Guéant, M. Hertl, G. Kanny, A. Kapp, M. Kidon, M. Kowalski, V. Kvedariene, D. Laroche, G. Marone, C. Mayorga, H. Merk, A.D. Moneret-Vautrin, C. Mouton, W. Pichler, C. Ponvert, B. Przybilla, E. Rebelo-Gomes, J. Ring, J. Rodrigues-Cernadas, A. Romano, F. Rueff, A. Sabbah, J. Sainte Laudy, M. Sanz, V. Soriano, E. Tas, E. Treudler, E. Tomaz, D. Vervloet, B. Wedi, B. Wüthrichm M. Yazicioglu.