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Immediate hypersensitivity to penicillins with negative skin tests – the value of specific IgE

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KEY WORDS

Allergy, penicillins, hypersensitivity reactions, predictive value, specific IgE, skin testing

SUMMARY

The determination of specific IgE in patients with history of penicillins hypersensitivity is simple, safe and widely available. The positive and negative predictive values of this determination, however, are not yet established. In order to evaluate them, we performed specific IgE determination and diagnostic drug challenges in a group of 22 patients with a clear history of immediate penicillins hypersensitivity but negative skin tests. In this sample, the positive and negative predictive values were 29% and 87%, respectively. This seems to indicate that a positive specific IgE is not enough to confirm the diagnosis, and further study is necessary.

Beta-lactams are the most commonly used antibiotics, accounting for 2/3 of those available on the market, and the most frequent cause of antibiotic hypersensitivity reactions. Among them, natural and semisynthetic penicillins are responsible for more than 75% of those episodes (1). Hypersensitivity reactions are a major health concern as they can be a significant cause of morbidity and mortality, limit therapeutic options and consequently alter the pattern of microbial resistances and increase socio-economic costs (2). For these reasons, the study of all suspected cases of penicillins hypersensitivity is highly important, to avoid the unnecessary use of less efficient or more expensive alternatives, due to fear of a reaction.

Currently, a firm diagnosis is based on a detailed clinical history, skin testing (prick and intradermal tests), specific IgE determination and drug challenge when the previous are both negative and the reaction is not life-threatening (3,4).

Several previous studies have focused in determining the sensitivity, specificity, positive and negative predictive value of skin tests for diagnosis of penicillins hypersensitivity reactions (5,6). The determination of specific IgE in patients with history of penicillins hypersensitivity is a simple, safe and widely available tool. To our knowledge, however, there has been no study concerning predictive values of specific IgE determination. This is of utmost importance in order to determine if a positive IgE in patients with history of penicillins hypersensitivity reaction makes drug challenge tests unnecessary. In a study by Blanca *et al* (7), 42% of 26 patients with negative skin tests and a positive drug challenge had positive specific IgE to benzylpenicilloyl or amoxicilloyl, suggesting that this subgroup of patients could have been diagnosed by specific IgE determination alone, obviating the need to challenge them. But this still does not answer the ques-

tion whether all patients with positive specific IgE are truly allergic without doing a drug challenge. Particularly troublesome are the cases with negative skin tests and positive specific IgE: is it a true or false-positive result? Another important question relates to patients with a clear hypersensitivity history but with both negative skin tests and specific IgE: can we be sure they really are not allergic without doing a provocation test?

Following a previous paper (8) about the diagnostic work-up in patients with history of beta-lactam hypersensitivity reactions, and to determine the positive and negative predictive values of specific IgE in patients with negative skin tests (prick and intradermal), we performed specific IgE determination and diagnostic drug challenge tests in a group of 22 patients (8 male, 14 female), with 40.4 ± 19.0 years of age and a clear history of penicillins hypersensitivity reactions but negative skin tests to PPL and MDM (or penicillin), amoxicillin and ampicillin. All patients had history of an immediate reaction, with a cutaneous presentation in 13 cases, respiratory in 3, cutaneous+respiratory in 4 and gastrointestinal in 2. The implicated antibiotics were penicillin and amoxicillin, with 11 cases each. Cut-off for IgE was considered 0.35 kU/L, with values above or equal this considered positive and those below it considered negative (UniCAP-System®, Phadia, Uppsala, Sweden). Out of the 22 tested patients, 7 had positive specific IgE to penicillin G or V, amoxicillin or ampicillin, with values ranging from 0.40 to 2.90 kU/L and the remaining 15 had negative specific IgE to the same antibiotics. In patients with positive IgE, the elapsed time between the IgE measurement and the drug challenge was, on average, 22 months (ranging from 6 to 41 months) and none of the previous reaction had been life-threatening. The drug challenge tests were done according to ENDA guidelines (4), under strict medical surveillance. Increasing doses (four or five), of the antibiotic to which the patients had positive specific IgE were administered each 30 min until the therapeutic dose was achieved. The symptoms and signs were monitored during the challenge, as well as pulse, blood pressure and PEF measurements. In order to evaluate non immediate reactions, patients stayed under medical surveillance for 3 hours after finishing the challenge and were instructed what to do if any reaction occurred after being dismissed from the hospital.

Of the 7 tested cases with positive specific IgE, only 2 had a positive reaction to the drug challenge, both immediate and with cutaneous involvement (similar to the previous reaction). The remaining 5 patients had no immediate nor late symptoms.

Of the 15 tested cases with negative specific IgE, 13 had no immediate nor late symptoms and only 2 had a positive reaction to the drug challenge, one of them immediate and the other delayed, both mild and non life-threatening.

Despite being a very small group of patients and keeping in mind the wide interval between in vitro IgE measurement and drug provocation test, it seems reasonable to question the positive predictive value of specific IgE in the diagnosis of penicillins hypersensitivity reactions since in our sample it was only of 29% (2 out of 7 patients). This seems to indicate that a positive specific IgE in patients with history of penicillins hypersensitivity but negative skin tests is not enough for confirming the diagnosis, and further study (challenge test) is mandatory. In a study by Petersen *et al* (9), the CAP-FEIA (Phadia) system showed that despite being highly sensitive, it is susceptible to false-positive results due to irrelevant specific IgE antibodies with low affinity and also to cross-reacting IgE. This may be the case in our study. However, we cannot exclude the hypothesis that a decrease in specific IgE levels over time, as has already been demonstrated (3,10), as an explanation for the low positive predictive value of positive specific IgE in these patients.

In contrast with the positive predictive value, the negative predictive value of specific IgE in patients with history of penicillins hypersensitivity but negative skin tests is much higher (13 out of 15 patients, 87%), and is probably enough to confirm the diagnosis of IgE-mediated allergy. More studies, with a larger number of patients and smaller time intervals between the IgE determination and drug challenge are needed to establish the real positive predictive value of positive specific IgE in patients with negative skin tests.

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