Reproducibility of delayed-type reactions to betalactams

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ABSTRACT

Background: Delayed reactions with betalactam antibiotics are a very common reason for consultation and a matter of numerous publications.

Objective: To demonstrate that delayed reactions occurring during treatment with betalactam antibiotics are not reproduced in a high percentage of the patients, when making drug challenge.

To analyse the characteristics of people showing this type of reaction.

Methods: We included in our study all the patients who came to our Allergy Department during one year (2004), with a clinical history of delayed reaction (> 72h) to betalactams. Skin prick tests (SPT), intradermal tests (IT) and patch tests were carried out, followed by simple blind placebo controlled drug challenge (SBPCDC) at hospital and home treatment with betalactams.

Results: We studied 23 patients (12 men and 11 women), average age 23.4 years old. SPT and patch test were negative in all patients. Only one patient showed positive IT tests, and allergic reaction was only reproduced in two patients; 76 % tolerated the drug involved in supposed allergy.

Conclusions: Simple blind oral challenge with implicated drug followed by home treatment is required for a conclusive diagnosis of allergy in patients with delayed reactions to betalactams.

Key words: Drug allergy. Betalactams. Delayed-type. Penicillins, SBPCDC.

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INTRODUCTION

Diagnosis of delayed-type reactions after treatment with betalactams, in particular Penicillins, continues to be a matter of numerous publications.

Allergic reactions to Penicillins have always been classified as immediate reactions (these occurring in the first hour after being administered); accelerated reactions (occurring between 1-72 hours) and delayed reactions (occurring after 72 hours)[1]. By general consent, they have been classified as Immediate (they occur during the first hour after the administration) and non-immediate (they would include both accelerated and delayed).

In delayed reactions, the immunological mechanism responsible is not totally known. Some studies point out that these types of reactions correspond to type IV reactions, measured by T cells[2], which makes diagnosis difficult. Clinical symptoms included within the delayed reactions range from skin symptoms: urticaria and maculopapular exanthema or rash, as the most frequent, to syndromes with an important systemic affectation.

In clinical practice we have the impression that delayed skin reactions following the administration of betalactams are not reproduced in a high proportion of cases. We performed this study with the aim of analysing the reproducibility of the delayed reactions to betalactams, gathered through clinical history in our out-patients clinic.

In order to make a correct diagnosis and check the reproducibility of these type of reactions, we followed the diagnostic algorithm proposed by Romano et al[3] including skin prick tests, intradermal test, patch tests and a SBPCDC.

MATERIAL AND METHODS

Selection of patients

All the patients who attended our Allergy department during one year (2004) with a history of delayed reaction (> 72 h) to betalactams were included in the study.

Skin tests

Prick and intradermal test[4]

We performed skin prick tests (SPT) on all patients, with the following agents: Penicillin (100,000 UI/ml), Benzylpenicilloyl polylysine (PPL) and minor determinants (MDM) (1.2 ml, dilution 1/10 of commercial preparation, supplied by Diater laboratories), amoxicillin (AX) (200 mg/ml), ampicillin (AMP) (200 mg/ml) and Cephalosporin (200 mg/ml) and in one of them, also cloxacillin (CLOX) (200 mg/ml) since it was the drug involved, considering positive the reactions of more than 3 mm in diameter. Histamine was used as a positive control (10 mg/ml), and as a negative control, a saline solution was used.

For intradermal tests (IT), the concentration was of 1000 UI/ml for Penicillin, PPL and MDM (1.33 ml, dilution 1/100) and 20 mg/ml for the rest, considering positive a papule of more than 5 mm after 15-20 minutes of its application in the early response, and 48 hours in the delayed response. Histamine was used as a positive control (1 mg/ml) and as a negative control, a saline solution was used.

Patch test

This was performed with the same agents as above at a concentration of 5 % in Vaseline (weight/volume), applied on the back and read after 48 and 96 h.

In vitro tests

Specific IgE to penicillin, amoxicillin, ampicillin and cephalosporine were assessed by CAP system (Phadia) in those patients with a reaction onset after 72h of starting treatment, but less than 2 hours from the intake of the last dose, in order to exclude the possibility of an IgE mediated mechanism.

Challenge test

Patients with negative cutaneous and in vitro test were challenged with the involved drug by means of simple-blind placebo-controlled drug challenge (SBPCDC). On the first day, a placebo challenge in several doses was performed. On the second day, the drug involved was administered reaching therapeutic doses, starting with an initial dose of 25 mg, followed by 50, 175 and 250 mg, with intervals of 30 minutes (accumulated dose 500 mg). In paediatric-age patients, the dose was adjusted according to age and weight.

If the SBPCDC was negative, the patient underwent home treatment with the involved drug with the same reported dose and schedule.

Ethical approval

All patients were verbally informed about the procedure, and signed a written informed consent. This informed consent was approved by the Hospital Scientific Ethics Committee, and it is periodically revised. This type of drug allergy study is part of our habitual work at the Allergy Department.

RESULTS

We studied 23 patients (12 men and 11 women) with an average age of 23.4 years (ranging 0.8 to 70 years old). In most patients (15) the adverse reaction had occurred throughout the year prior to the study. The involved drug, according to reported clinical history, was amoxicillin-clavulanic in 11 patients (47.8 %), AX in 10 patients (43.4 %) cloxacillin in 1 patient (4.3 %) and penicillin in 1 patient (4.3 %) (Table I). The different clinical symptoms were urticaria in 7 patients (30.5 %), exanthema in 11 patients (47.8 %), angioedema in 2 patients (8.7 %) erythema in 1 patient (4.3 %) and another type of reaction in 2 patients (8.7 %) (Table I).

SPT were negative in all patients. IT were negative in all patients except in one of them (patient 12), who