Reproducibility of delayed-type reactions to betalactams

M. Rodriguez-Alvarez, S. Santos-Magadan, B. Rodriguez-Jimenez, I. Reig-Rincon de Arellano, S. Vazquez-Cortes and **C. Martinez-Cocera**

Allergy Department. Hospital Clínico San Carlos. Madrid. Spain.

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.

Correspondence:

Dr. Sara Santos Magadán
Allergy Department
Hospital Clínico San Carlos
Profesor Martín Lagos, s/n
28040 Madrid. Spain.
Tel.: 0034-91 330 3012/0034-676 32 50 42

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

Table I

Results reported in history: Patients' characteristics and reactions

Patient	Age	Sex	Drug	Latency time	Type of reaction
1	60	M	AX-CLAV	> 5 d	U
2	68	M	AX-CLAV	3-4 d	O
3	50	F	AX-CLAV	4-5 d	U
4	44	F	AX-CLAV	4-5 d	AE
5	9	F	AX-CLAV	3-4 d	AE
6	5	M	AX-CLAV	> 5 d	EX
7	1	M	AX	> 5 d	EX
8	3	M	AX-CLAV	3-4 d	EX
9	8	M	AX	> 5 d	EX
10	0,8	F	AX	> 5 d	EX
11	1,8	F	AX-CLAV	3-4 d	EX
12	1,5	M	AX	3-4 d	ER
13	27	M	AX	3-4 d	EX
14	2	M	AX	3-4 d	EX
15	9	M	PENICILLIN	3 d	EX
16	19	M	AX-CLAV	> 5 d	EX
17	34	F	AX	3-4 d	U
18	24	F	CLOXACILLIN	> 5 d	O
19	32	M	AX	3-4 d	FE
20	18	F	AX-CLAV	3-4 d	U
21	14	F	AX-CLAV	> 5 d	U
22	70	F	AX	> 5 d	U
23	37	F	AX	> 5 d	U

M: Male; F: Female; Ax: Amoxicillin; Ax-Clav: Amoxicillin-Clavulanic.
Type of reaction: U: Urticaria; AE: Angioedema; E: Exanthema; FE: Fixed Exanthema; O: Others; Er: Erythema.

Table II

Results of in vivo tests

Patient	ID	PT	Drug	Hospital reaction	Days at home	Home reaction
1	(–)	(–)	AX-CLAV		5 d	
2	(–)	(–)	AX-CLAV		4 d	
3	(–)	(–)	AX		5 d	
4	(–)	(–)	AX-CLAV		5 d	
5	(–)	(–)	AX-CLAV		7 d	
6	(–)	(–)	AX-CLAV		6 d	
7	(–)		AX		7 d	
8	(–)	(–)	AX-CLAV		5 d	
9	(–)		AX		7 d	
10	(–)		AX		5 d	
11	(–)		AX-CLAV		5 d	
12	POSITIVE					
13	(–)		AX		5 d	U
14	(–)		AX	ERYTHEMA		
15	(–)	(–)	PENICILLIN		3 d	EX
16	(–)	(–)	AX-CLAV		5 d	
17	(–)		AX		4 d	
18	(–)		CLOXACILLIN		5 d	
19	(–)	(–)				
20	(–)	(–)	AX-CLAV		7 d	
21	(–)	(–)	AX-CLAV		2 d	U
22	(–)		AX		5 d	
23	(–)	(–)	AX		5 d	

Ax: Amoxicillin; Ax-Clav: Amoxicillin-Clavulanic.
Type of reaction: U: Urticaria; AE: Angioedema; E: Exanthema; FE: Fixed Exanthema; D: Dyspnoea; O: Others; Er: Erythema.

presented a positive intradermal test with cephalosporine (8 mm), amoxicillin (6 mm) and MDM (5 mm) in the early response.

In the rest, the IT were negative, both in the early and delayed reading, including the three patients diagnosed with allergy to betalactams, after a positive challenge (patients 14, 15 and 21).

Patch tests (PT) were negative in all the patients to whom they were applied (13 patients), including two patients who were diagnosed with allergy to betalactams after the challenge (patient 15 and 21). On patient 19, who reported symptoms suggestive of Fixed Exanthema after administration of amoxicillin, in two consecutive occasions (diagnosed by clinical history) both IT and PT were negative.

Specific IgE to betalactams was determined in 14 patients with a negative result (< 0.35 kU/L) in all of them.

Patients who had presented positive in vitro or in vivo tests were not challenged due to ethical reasons.

SBPCDC was finally carried out in a total of 21 patients. On the first day, a placebo was given and no patient had any adverse reaction. On the second day, the drug involved was administered reaching therapeutic doses, and only one patient reacted (patient 14), showing intense erythema on face and neck a few minutes after the first dose administration.

Home treatment with the involved drug, with the same reported dose and schedule, was given to the remaining patients (20), having a negative result on the SBPCDC (Table II).

Three paptients had a positive home drug challenge. In two of them the clinical symptoms were reproduced: exanthema by penicillin (patient 15) after 3 days of treatment, and urticaria by Ax-Clav (patient 21), but only after 2 days of treatment. The third patient developed urticaria when the previous reaction was an exanthema (patient 13).

In conclusion, both the time of appearance and clinical symptoms were only reproduced in one of

the patients (exanthema by Penicillin 72 h after treatment, patient 15).

DISCUSSION

In our study, exclusive cutaneous reactions appear as the most frequent manifestations of non-immediate reactions after the administration of betalactamic antibiotics and, as in previous studies, aminopenicillins are the most frequent cause for this type of reactions[5].

Besides hypersensitivity reactions, numerous mechanisms have been proposed as causative for this type of reactions. Viral infections have been widely studied[6] and bacterial infections have also been related with their appearance[7].

Metabolic factors, immunological and genetic factors, have been related to delayed cutaneous reactions after the administration of different antibiotics[8].

The diversity of the possible ethiologies, as well as the absence of relation with IgE mediated mechanism, makes it difficult to diagnose patients who present this type of reactions.

In recent years, different tests for the diagnosis of non-immediate reactions have been evaluated. IT and PT appear in the literature as valid techniques for the diagnosis of non-immediate reactions after the administration of penicillins[9,10]; the sensitivity of the IT seems to be higher than the PT for the diagnosis of non-immediate reactions[11], and the results of the skin test, do not seem to be influenced by the time interval between the last adverse reaction and the allergy test[3].

Although the importance of IT delayed readings has been reported in the literature[1], none of our patients had a positive delayed reaction on IT, including those who had a positive result on SBPCDC.

In view of a positive result in the cutaneous test, administration of betalactamic antibiotics must be avoided[3], but in a high percentage of patients, with a reported history compatible with delayed reaction, we came across a negative result for both tests.

In our study, 13 % of patients with a negative result for IT and PT presented reactions after administrating the drug involved again, when following the same schedule and dose that prompted the reaction.

In patients with a clinical history suggestive of delayed allergic reactions due to betalactams, and negative result in the cutaneous tests, SBPCDC is necessary for a certain diagnosis.

In literature reports, this challenge was proposed to be developed through a progressive increasing dose, over several weeks until the therapeutic dose has been reached, to check the drug's tolerance[3].

In our study, the challenge was performed with the involved drug, reaching therapeutic doses on the first day at hospital, under supervision of trained personnel. Once the absence of immediate reaction had been confirmed, home treatment was established with the involved drug, with the same number of days that had previously produced the reaction.

This criterion has proved to be safe and efficient in our regular clinical practice, in patients with exclusive cutaneous symptoms.

To conclude, in those patients with exclusive cutaneous manifestations and negative in vitro and in vivo tests, we propose the administration of the implied drug through SBPCDC until therapeutic dose in one day at hospital, followed by home treatment with the same dose and schedule that produced the reported reaction, as this criteria has proven to be safe and efficient to establish a definitive diagnosis.

REFERENCES

1. Levine BB. Immunologic mechanisms of penicillin allergy: A haptenic model system for the study of allergic diseases of man. N Engl J Med. 1966;275:1115-25.
2. Werner J Pichler. Delayed drug hipersensitivity reactions. Ann Intern Med. 2003;139:683-693.
3. Reig Rincón de Arellano I, Villalón García AL, Cimarra Alvarez-Lovell M,Robledo Echarren T, Martínez Cócera MC. Flare up to betalactams. Allergol Immunopathol (Madr). 2005 Sep-Oct; 33(5):282-4.
4. Torres MJ, Blanca M, Fernández J, Romano A, Weck A, Aberer W et al.; EAACI Interest Group on Drug Hypersensitivity. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003; 58:962-72.
5. Terrados S, Blanca M, García J, Vega J, Torres MJ, Carmona MJ, et al. Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. Allergy. 1995;50:563-567.
6. Renn CN, Straff W, Dorfmuller A, Al-Masaoudi T, Merk HF, Sachs B. Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. Br J Dermatol. 2002 Dec; 147(6): 1166-70.
7. Cohen AD, Friger M, Sarov B, Halevy S. Which intercurrent infections are associated with maculopapular cutaneous drug reactions? A case-control study. Int J Dermatol. 2001 Jan; 40(1):41-4.
8. Riley RJ, Leeder JS. In vitro analysis of metabolic predisposition to drug hypersensitivity reactions. Clin Exp Immunol. 1995 Jan; 99(1):1-6.
9. Patriarca G, D'Ambrosio C, Schiavino D, Larocca LM, Nucera E, Milani A. Cinical usefulness of patch and challenge tests in the diagnosis of cell-mediated allergy to betalactams. Ann Allergy Asthma Immunol. 1999 Sep; 83(3):257-66.
10. Torres MJ, Sanchez-Sabaté E, Álvarez J, Mayorga C,Fernandez J,Padial A et al. Skin test evaluation in nonimmediate reactions to penicillins. Allergy. 2004; 59:219-224.
11. Romano A,Quarantino D,Di Fonso M,Papa G,Venuti A,Gasbarrini G. A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins. J Allergy Clin Immunol. 1999; 103:1186-90.