

*Immediate allergic reactions to amoxicillin

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A large group of patients with suspected allergic reactions to β -lactam antibiotics was evaluated. A detailed clinical history, together with skin tests, RAST (radioallergosorbent test), and controlled challenge tests, was used to establish whether patients allergic to β -lactam antibiotics had selective immediate allergic responses to amoxicillin (AX) or were cross-reacting with other penicillin derivatives. Skin tests were performed with benzylpenicilloyl-poly-L-lysine (BPO-PLL), benzylpenicilloate, benzylpenicillin (PG), ampicillin (AMP), and AX. RAST for BPO-PLL and AX-PLL was done. When both skin test and RAST for BPO were negative, single-blind, placebo-controlled challenge tests were done to ensure tolerance of PG or sensitivity to AX. A total of 177 patients were diagnosed as allergic to β -lactam antibiotics. We selected the 54 (30.5%) cases of immediate AX allergy with good tolerance of PG. Anaphylaxis was seen in 37 patients (69%), the other 17 (31%) having urticaria and/or angioedema. All the patients were skin test negative to BPO; 49 of 51 (96%) were also negative to MDM, and 44 of 46 (96%) to PG. Skin tests with AX were positive in 34 (63%) patients. RAST was positive for AX in 22 patients (41%) and to BPO in just 5 (9%). None of the sera with negative RAST for AX were positive to BPO. Challenge tests with AX were performed in 23 subjects (43%) to establish the diagnosis of immediate allergic reaction to AX, and in 15 cases (28%) both skin test and RAST for AX were negative. PG was well tolerated by all 54 patients. We describe the largest group of AX-allergic patients who have tolerated PG reported so far. Diagnosis of these patients can be achieved only if specific AX-related reagents are employed. Further studies are necessary to determine the exact extent of this problem and to improve the efficacy of diagnostic methods.

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The penicillins are a major and widely used group of antibiotics and have been shown, in extensive clinical use, to have low toxicity (20). In spite of this, they are the commonest cause of drug-induced allergic reactions, including anaphylaxis (27), and although the true incidence is difficult to assess, there is a significant clinical problem (12). Several major clinical studies have confirmed that skin testing with the appropriate reagents is a safe and effective procedure to diagnose immediate reactions to benzylpenicillin (PG) (19, 24, 26), and the radioallergosorbent test (RAST) to detect antibodies against the major determinant of PG (benzylpenicilloyl) is

also a useful diagnostic aid (14, 17, 32). However, acceptable skin tests and RAST for the other β -lactam antibiotics are not commercially available. Studies have shown that the degree of cross-reactivity of β -lactam compounds probably varies among subjects (4, 5). Worldwide, amoxicillin (AX) is one of the most widely prescribed β -lactam antibiotics in both in- and outpatient clinics. Previous studies by our group described patients who were allergic to AX but could not be diagnosed by standardized diagnostic procedures. Moreover, these patients tolerated the administration of PG. In this work, we present a large group of patients who experienced immediate reactions to AX but who tolerated PG. We analyze the total number of penicillin-allergic subjects and describe the clinical characteristics, skin tests, and RAST in the AX-selective group.

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Material and methods

Between January 1987 and June 1991, we undertook an observational study of patients who had been referred to the Allergy Section of Carlos Haya Regional Hospital, Málaga, Spain, after suspected allergy problems during treatment with penicillins. Studies included a detailed history of suspected adverse reactions to these drugs, together with skin tests, RAST, and controlled challenge tests to assist the diagnosis. The possible risks of diagnostic procedures were explained to the patients, and written informed consent was obtained before studies commenced.

Patients

Positive group. From all our patients diagnosed as allergic to β -lactam antibiotics, we selected only those with a history of immediate allergic reactions (anaphylaxis or urticaria-angioedema) to AX and good tolerance of PG. Diagnosis of AX-induced allergy was confirmed by skin test and/or AX-RAST, or, where these tests were negative, by immediate positive challenge test with AX. Tolerance of PG was demonstrated by challenge test.

Negative control group. Thirty subjects with no previous allergic reactions to drugs were selected to study the nonspecific irritant capacity of each skin test solution, and their sera were used to establish the RAST cutoff point.

Skin tests

Procedures. Skin tests were normally performed by injecting 0.02 ml of the testing material intradermally into the volar area of the forearm. In extremely sensitive patients, several times lower dilutions or prick tests were used initially. Tests were read 15 min later. A wheal equal to or greater than the histamine wheal was considered to be positive. A wheal 50–100% of the histamine wheal was interpreted as doubtful.

Reagents. The concentrations and reagents used in skin tests were as follows: 1) benzylpenicilloyl-poly-L-lysine (BPO-PLL) 5×10^{-5} M (Laboratoires des Stallergens, Fresnes, France); 2) MDM: benzylpenicilloate sodium salt plus PG, final concentration 10^{-2} M (Laboratoires des Stallergens, Fresnes, France); 3) PG 10000 IU/ml (Antibióticos SA, León, Spain); 4) ampicillin (AMP) 20 mg/ml (Normon SA, Madrid, Spain); 5) AX 20 mg/ml (Beecham Pharmaceuticals, London, UK); 6) histamine phosphate 0.1 mg/ml (Alergia e Inmunología Abelló SA, Madrid, Spain); 7) normal saline (Baxter SA, Valencia, Spain).

RAST assays

Cyanogen-bromide-activated cellulose disks (Filter paper 54, Whatman International, Maidstone, UK) were coupled to PLL and then treated with PG and AX as described (11). The tests were performed as previously reported (29). The RAST results reflect the radiolabeled substance uptake, expressed as a percentage of the maximum counts per minute (cpm) added. Values over the mean + 2 SD of the results in the negative control group for BPO and AX were considered to be positive.

Challenge tests

Single-blind, placebo-controlled challenge tests were done to ensure tolerance of PG or sensitivity to AX. One million IU of PG was administered by the intramuscular route. If there was no reaction and diagnosis of allergy to AX was not certain from clinical history and skin tests and/or RAST, then AX was given the following week by the oral or parenteral routes, starting with 5 mg and increasing progressively to 500 mg unless a reaction occurred. The protocol for challenge tests was approved by the hospital ethics committee.

Results

Between January 1987 and June 1991, 177 patients were diagnosed as allergic to β -lactam antibiotics. Of these, 146 (82.5%) were immediate reactions, and 31 (17.5%) were nonimmediate. Following the selection criteria, we selected the 54 cases of immediate AX allergy with good tolerance of PG (30.5% of total). None of the others met the selection criteria (36 patients who had allergic reactions after AX administration showed either positive skin tests or positive challenge to BP; 42 were initially sensitized to PG, etc.).

Clinical history data. Table 1 shows the clinical history data for the 54 patients studied, including the drug involved in the original allergic reaction and the resulting clinical symptoms. The mean age of the patients was 34 years (range 14–70); 28 were female and 26 male. AX was the most frequently involved drug (42 cases, 78%). AX plus clavulanic acid compound was responsible in six cases (11%) and AMP in four (7%), with two unknown.

Anaphylaxis was seen in 37 patients (69%). In 12 of them (nos. 3, 12, 15, 21, 23, 27, 34, 37, 38, 39, 43, 46), hypotension was verified in emergency rooms. The other 17 cases (31%) had urticaria and/or angioedema.

Table 1. Clinical history data

Patient no.	Age	Sex	Drug	Reac.	Patient no.	Age	Sex	Drug	Reac.
1.	25	M	AX	A	28.	33	F	AX	A
2.	35	M	AX	A	29.	35	F	AX	UA
3.	22	F	AX	A	30.	37	M	AX	UA
4.	62	M	AX	A	31.	27	F	AX	A
5.	25	F	AX	A	32.	32	F	AX	A
6.	18	F	AX	A	33.	35	F	AX	A
7.	22	M	AX	UA	34.	28	M	AX	A
8.	43	F	AX	UA	35.	41	M	AX	A
9.	38	F	AX	UA	36.	53	F	AX	A
10.	31	M	U	UA	37.	15	M	AX	A
11.	42	M	AMP	A	38.	55	M	AX	A
12.	34	F	AX	A	39.	40	M	AX	A
13.	49	M	AMP	A	40.	21	F	AX	UA
14.	28	M	AX	A	41.	36	M	AX	A
15.	30	M	AMP	A	42.	33	F	U	UA
16.	41	M	AX	A	43.	38	M	AX-CL	A
17.	33	F	AX	UA	44.	49	M	AX	A
18.	65	M	AX	A	45.	17	M	AX	A
19.	20	F	AX-CL	UA	46.	32	F	AX	A
20.	30	M	AX	UA	47.	60	F	AX	A
21.	36	M	AMP	A	48.	21	F	AX	UA
22.	29	F	AX-CL	A	49.	33	F	AX	UA
23.	34	M	AX	A	50.	14	F	AX	UA
24.	25	F	AX	UA	51.	19	F	AX	UA
25.	36	M	AX-CL	A	52.	18	F	AX	A
26.	37	F	AX-CL	A	53.	43	M	AX	A
27.	54	F	AX	A	54.	50	F	AX	UA

U: unknown; AX-CL: amoxicillin plus clavulanic acid; A: anaphylaxis; UA: urticaria-angioedema.

Skin tests. Skin tests and RAST results are shown in Table 2. None of the 30 subjects in the negative control group showed positive reactions to any determinants used in the skin tests. All the patients were also skin test negative to BPO. Forty-nine of 51 (96%) were also negative to MDM, and 44 of 46 (96%) to PG. Only two patients in these two tests (MDM and PG) had doubtful results. Skin tests with AMP were positive in 9 of 47 cases (19%), negative in 34 (72%), and doubtful in 4. None of the positive results were positive to AMP alone.

Skin tests with AX were positive in 34 (63%) patients. None of the patients with negative skin tests for AX were positive for other skin test reagents. In nine patients (17%) (nos. 6, 10, 15, 26, 27, 34, 35, 38, 40), skin testing with AX elicited systemic reactions (Table 3). In two patients (nos. 1, 41), wheals of AX skin tests were greater than 200% of histamine wheal, and pseudopodic prolongations appeared. Two other cases showed doubtful results.

RAST (Table 2). Values over 1.4% of maximum cpm added for BPO and over 1.1% for AX were considered to be positive (these figures were the results of the mean plus 2 SD of the negative control group). RAST was positive for AX in 22 patients (41%) and for BPO in only five (9%). None of the sera with negative RAST results for AX were positive for BPO.

Challenge tests. Results of challenge tests are shown in Table 4. PG was well tolerated by all patients. Challenge tests with AX were performed in 23 cases (43%) to establish the diagnosis of immediate allergic reaction to AX. In 15 cases (28%), both skin test and RAST to AX were negative. All challenge tests were positive within 45 min of AX administration. AX was given by mouth in most cases. Generalized pruritus and erythema were the most frequent reactions, although tachycardia, chest tightness, urticaria, angioedema, and malaise also appeared. Only one patient showed hypotension in controlled challenge tests, and all subjects recovered within 60 min after treatment was started.

Discussion

The chemical structure of AX differs from PG only in the side-chain, where AX contains additional α -amino and *p*-hydroxy groups (10). Using monoclonal antibodies, de Haan et al. (9) have shown that the side-chain can be recognized as a unique epitope. Other reports have highlighted the importance of the side-chain in cross-reactivity of penicillins (23), cephalosporins (4, 21), and monobactams (1).

For years, it has been accepted that, in allergic reactions to penicillins, skin testing with major and minor determinants of PG is virtually predictive of new reactions (13, 18, 22, 30, 31), although different

Table 2. Results of skin test and RAST

Patient no.	Skin test					RAST	
	BPO	MDM	PG	AMP	AX	BPO	AX
1.	-	-	-	+	+	0.4	0.3
2.	-	-	-	-	+	0.2	0.5
3.	-	-	-	-	-	0.7	0.3
4.	-	-	-	-	-	0.2	0.2
5.	-	-	-	-	+	1.1	2.0
6.	-	-	-	+	+	6.1	11.3
7.	-	-	-	-	-	0.3	0.4
8.	-	±	±	±	+	0.3	0
9.	-	-	-	-	-	0	0
10.	-	-	-	+	+	0.8	1.3
11.	-	-	-	-	-	0.9	0.5
12.	-	-	-	-	+	0.2	0.3
13.	-	-	-	-	±	0.6	0.2
14.	-	-	-	-	+	4.1	24.9
15.	-	-	-	±	+	0	0
16.	-	±	±	+	+	0	0
17.	-	-	-	+	+	0.6	1.3
18.	-	-	-	-	+	1.3	5.7
19.	-	-	-	-	-	0.6	0.8
20.	-	-	-	-	-	0.1	1.2
21.	-	-	-	-	+	1.3	4.9
22.	-	-	-	-	+	1.1	9.3
23.	-	-	-	±	+	0.4	0.3
24.	-	-	-	-	+	0.9	0.8
25.	-	-	-	-	-	0.2	0.1
26.	-	-	-	-	+	0.9	0
27.	-	-	-	+	+	0.6	0.6
28.	-	-	-	-	-	2.6	1.2
29.	-	-	-	-	+	0.4	20.7
30.	-	-	-	+	+	7.1	23.1
31.	-	-	-	-	±	0.2	0.7
32.	-	-	-	±	+	3.9	1.3
33.	-	-	-	-	-	0.3	0.6
34.	-	-	-	-	+	1.2	9.5
35.	-	-	-	-	+	1.2	2.6
36.	-	-	-	-	-	0.8	0.5
37.	-	-	-	-	+	0	4.7
38.	-	-	-	-	+	0	25.1
39.	-	-	-	-	+	0.4	0.6
40.	-	-	-	-	+	0.6	2.8
41.	-	-	-	+	+	0.8	0.6
42.	-	-	-	-	+	1.0	3.5
43.	-	-	-	-	+	0	0
44.	-	-	-	-	+	0	1.4
45.	-	-	-	-	+	0.4	1.5
46.	-	-	-	+	+	0.1	0.1
47.	-	-	-	-	+	0.4	0.3
48.	-	-	-	-	-	0.8	0.2
49.	-	-	-	-	-	0.2	0.6
50.	-	-	-	-	-	0	0.1
51.	-	-	-	-	-	0.3	0.1
52.	-	-	-	-	-	0.5	0.6
53.	-	-	-	-	-	0.5	6.2
54.	-	-	-	-	-	0.2	0.3

* Wheal > 5 cm; sr: systemic reaction; ± = doubtful.

Values (boldface) over 1.4 for BPO and 1.1 for AX were considered to be positive.

Table 3. Systemic reactions to intradermal skin tests with amoxicillin

Patient no.	Systemic reaction
6.	GP, chest tightness and nausea
10.	GP, GE and dysphonia
15.	GP and ↓ BP
26.	GP and GE
27.	Facial erythema and lip angioedema
34.	GE and tachycardia
35.	GP and GE
38.	GP, GE, ↓ BP, and tachycardia
40.	GP, facial and shoulder erythema

All skin tests were made by intradermal route at 20 mg/ml except patient 40 at 0.2 mg/ml. ↓ BP: drop in blood pressure; GP: generalized pruritus; GE: generalized erythema.

Table 4. Challenge tests with amoxicillin

Patient no.	Reaction
3.	GP, GE, ↓ BP, 15 min after 5 mg AX po
4.	GP, GE, 10 min after 50 mg AX po
7.	Lip angioedema, facial pruritus, 30 min after 500 mg AX
9.	GP, GE, urticaria, 45 min after 500 mg AX po
11.	Urticaria after 100 mg AX po
13.	GP, GE, tachycardia, 15 min after 50 mg AX sc
16.	GP, GE, malaise, 10 min after 20 mg AX sc
17.	GP, GE, arm urticaria, 20 min after 250 mg AX po
19.	Tingling of tongue, tachycardia, 20 min after 50 mg AX
20.	GP, GE, anxiety, 25 min after 100 mg AX po
25.	GP, GE, urticaria, 40 min after 100 mg AX po
28.	GP, facial erythema, malaise, 30 min after 5 mg AX
31.	GP, GE, malaise, 5 min after 50 mg AX sc
33.	GP, GE, arm and leg urticaria 20 min after 250 mg AX
36.	GP, GE, facial angioedema 20 min after 500 mg AX po
47.	GP, GE, tachycardia, 20 min after 5 mg AX po
48.	GP, facial erythema, 30 min after 100 mg AX po
49.	GP, urticaria, 20 min after 500 mg AX po
50.	GE, tingling of tongue, 20 min after 100 mg AX po
51.	GP, GE, urticaria, 15 min after 250 mg AX po
52.	GP, GE, 20 min after 200 mg AX po
53.	GP, GE, chest tightness, nausea, 10 min after 500 mg AX po
54.	GP, GE, urticaria, 45 min after 125 mg AX po

All patients tolerated PG administration.

↓ BP: drop in blood pressure; GP: generalized pruritus; GE: generalized erythema; po: *per os* (orally); sc: subcutaneously.

were conducted (8). Our group, for example, has reported BPO skin-test- and RAST-negative patients who presented both immediate and delayed allergic reactions to AX (6–8).

In this paper, we present a group of 54 subjects with selective intolerance of AX and good tolerance of PG who had previously suffered immediate reactions to β -lactam antibiotics; hence the high number of anaphylactic cases. We deliberately chose patients who had experienced immediate reactions to obtain a more homogeneous patient group. Immediate reactions are usually caused by IgE antibody (31), whereas nonimmediate reactions have various causes. Although the patients had originally suffered severe and life-threatening reactions (12 cases of

views have been reported (7, 24). These differences may be related to the pattern of β -lactam antibiotic consumption in the populations where these studies

anaphylactic shock), none of the 54 patients had a positive skin test for BPO or MDM (Table 2). We should point out that life-threatening reactions have developed after oral intake of AX, although this is accepted as the route with the least risk (2, 3).

Skin test for AX was positive in 63% of patients (34 of 54). This figure is similar to other data reported by our group with MDM of PG (5) and seems to be higher than figures reported by others (26). Use of BPO-PLL alone has been reported to identify up to 80% of PG-allergic patients (22, 31), and additional use of MDM could exclude 99.5% of subjects at risk of an immediate reaction if given penicillin (24, 25). Differences in sensitivity between AX and BPO skin tests might be related to the use of BPO coupled to PLL. According to our results, however, from the point of view of skin testing, if AX is not included, 63% of patients in this group may be diagnosed as not allergic to β -lactam antibiotics. Therefore, they could suffer life-threatening reactions on subsequent exposure to AX or perhaps to other, related antibiotics. It is important to note that 16% of patients developed systemic reactions after skin testing, demonstrating the risk of skin tests and the convenience of beginning with lower concentrations.

Skin tests for AMP were positive in nine cases and borderline in four. In all these subjects, skin tests were positive for AX. Furthermore, in cases where patients were positive by skin test for AMP, the drug involved in inducing the reaction was AX except for patient 10, where the drug was not known, and patient 15, where the drug was AMP (Tables 1 and 2). However, these two patients developed systemic reactions after skin testing with AX, suggesting that the primary drug involved could have been AX.

RAST for BPO detects PG-allergic patients adequately; this is as specific as a skin test but slightly less sensitive (14, 15, 17). In our patient group, 22 (41%) sera were positive in AX RAST (Table 3). The specificity of IgE detected by this RAST system has been demonstrated previously (6). Three patients proved to be skin test negative for AX but had positive RAST. Six of the positive AX RAST cases developed systemic symptoms with AX skin test, and four patients challenged with AX exhibited positive reactions, confirming the specificity of AX RAST. Only five sera were positive for BPO by RAST, and all of these were positive in the AX RAST. Since all of these patients were negative for BPO skin tests and PG challenge, it is possible that the BPO RAST results were caused by cross-reaction with AX antibody. Positive BPO RAST results and negative skin test for BPO have been reported by other authors (16).

In this study a surprising number of cases (28%) required challenge tests to establish a definite diag-

nosis, since both skin tests and RAST were negative in spite of an anaphylactic response to AX. This proportion of negative skin reactors seems to be very high, and it contrasts with the current evidence (reviewed by Weiss & Adkinson (31)).

Mention should be made of the role played by AMP in our group of cases. Solley et al. reported evidence of cases positive for AMP (24). Recently, other authors have presented data with MDM of AMP where 38% of the positive reactor group was skin test positive only to this metabolite (2, 3); however, in this latter study, AX was not included in all the patients. In our group, in no case was AMP able to induce a positive response by itself; patients always responded to AX as well.

Diagnosis of patients with allergic reactions to AX and good tolerance of other penicillins appears to be on the increase. It is reasonable to suppose that the prevalence of these reactions is high, and the situation may be similar in other countries where AX is widely used. In this work, we describe the largest group of specific AX-allergic patients reported so far. We show that AX allergy diagnosis can be achieved only if specific AX-related reagents and tests are employed. Further studies are necessary to determine the exact extent of this problem and to improve the efficacy of diagnostic methods.

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