

Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin

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A group of 34 penicillin-allergic patients was studied to determine skin test reactivity to the different penicillins involved in inducing the allergic reaction and the cross-reactivity with side-chain-related and side-chain-unrelated cephalosporins. All the subjects selected for the study had to be skin test positive to at least one of the following determinants: benzyl-penicilloyl-polylysine (BPO-PLL), minor-determinant mixture (MDM), amoxicillin (AX), or ampicillin (AMP), or to possess *in vitro* IgE to the following conjugates: benzyl-penicilloyl-human-serum albumin (BPO-HSA), ampicilloyl-human-serum albumin (AMP-HSA), and amoxicilloyl-human-serum albumin (AX-HSA). Cephalexin (CE) and ceftazidime (CEF) were used to assess cross-reactivity. If skin tests to any of these compounds were positive, the patient was considered to be allergic; if negative, a challenge test was performed. Sixteen patients (47%) were skin test positive to BPO and/or MDM, and nine (26%) exclusively to AX and/or AMP. In three cases (8%), the RAST was positive although the skin test was negative; one to BPO-HSA and two to AX-HSA and AMP-HSA. Six patients (17%) needed to be challenged with the penicillin involved to establish the diagnosis. In five patients (14%), the skin tests were positive to CE and in none to CEF. In all the others, the skin tests were negative to both cephalosporins, and the patients tolerated the drugs when challenged. These results indicate the relevance of side-chain-specific minor determinants in betalactams allergy and provide support for the role of this chemical structure in the evaluation of cross-reactivity between penicillins and cephalosporins.

Key words: allergy; cephalosporin; cross-reactivity; penicillin; side chain.

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Betalactam antibiotics are globally distributed compounds used to treat various infectious diseases. Allergic reactions are the most serious adverse effects induced by these compounds, and in some instances these reactions may even be life-threatening. Penicillin allergy has been studied profoundly and has been considered to be the model for drug allergy (3, 13, 22). The classical reagents BPO and MDM have been recommended for the diagnosis of allergic conditions to penicillin, and they are widely used (3, 13), although recent evidence indicates that the addition of amoxicillin (AX) and ampicillin (AMP) can im-

prove the diagnostic efficiency (2, 7, 18). Whether other semisynthetic penicillins are of diagnostic value has not yet been established, but in the presence of a negative skin test, the use of the drug directly involved may be necessary (2). We studied a group of 34 patients allergic to different semisynthetic penicillins and showed that the addition of AX and AMP can be of diagnostic value. Moreover, when cross-reactivity is taken into account, the use of similar side-chain cephalosporin indicates that in cases with a positive skin test a situation of *in vivo* cross-reactivity may be predicted.

Material and methods

Subjects. All the patients participating in the study were referred to our outpatient clinic for evaluation of allergy to betalactams. The criteria for inclusion in the study were as follows: history of allergy to penicillin plus either positive skin test or RAST. If, therefore, in spite of a definite history, both skin test and RAST to all the determinants used and described below were negative, then a challenge was performed to confirm penicillin allergy at the moment the study was undertaken.

Skin tests. Intradermal skin tests were performed on the volar side of the forearm with AX, AMP, benzyl-penicilloyl-polylysine (BPO-PLL), minor-determinant mixture (MDM), cephalexin (CE), and ceftazidime (CEF). The concentrations used are summarized in Table 1. These concentrations were shown to be specific and nonirritant by testing in a negative control group of 50 subjects.

In vitro tests (RAST assay). Specific IgE to BPO-human-serum albumin (HSA), AX-HSA, and AMP-HSA was determined in serum by Phadebas RAST (Pharmacia, Uppsala, Sweden) according to the instructions of the manufacturer. AMP-HSA and AX-HSA disks are commercially available for research use.

Challenge test. In subjects where both *in vivo* and *in vitro* tests were negative, challenges were performed with the drug involved until therapeutic doses were reached.

In six patients (17%), in spite of a suggestive history, both skin tests and RAST were negative. Therefore, a challenge to AX (the involved drug in all cases) had to be performed to establish the diagnosis. Patients 11, 21, and 34 presented an immediate cutaneous reaction, 10–20 min after taking 125, 250, and 50 mg AX, respectively. The other three patients (nos. 17, 18, and 27) experienced urticaria and/or angioedema exclusively, several hours after the administration of therapeutic doses of AX (cumulative doses of 850 mg).

Only the patients with negative skin test to CE and CEF were challenged. When skin test to any of

these drugs was positive, no challenge was undertaken. Oral CE and intravenous CEF were administered in progressively increasing doses from 10 and 1 mg, respectively, up to 500 mg, every 30 min. Each patient was carefully monitored during the study, and adequate equipment for attending to any adverse reaction was on hand.

The study was approved by the hospital ethics committee and prior informed consent was obtained from each patient participating in the study.

Results

Thirty-four patients allergic to penicillins were studied. Seventeen were males and 17 females. The ages ranged from 12 to 72 years. The number of allergic episodes reported was 48. In the subjects in whom the allergic episode occurred twice, penicillin and AX were the responsible agents in each episode (Table 2). In one case, the offending betalactam was unknown. AX induced the reaction in 58% of the cases, AMP in 20%, and BP in 18%. This represents a figure for aminopenicillins as a group of 78%.

Skin test results are shown in Table 3. In 25 patients, the skin tests were positive to at least one of the different determinants used. A heterogeneous pattern of skin positivity appeared, with five patients positive to AMP and AX. Different combinations of the determinants were observed in the rest (Table 3). With regard to the skin test reactivity to common or side-chain-specific determinants, 16 patients were positive to BPO-PPL and/or MDM and 19 to AX and/or AMP. RAST was positive in 11 patients to BPO-HSA, in nine to AMP-HSA, and in six to AX-HSA. When only the patients RAST positive but skin test negative were considered, there were three, with 28 patients both RAST and skin test positive.

Skin and challenge tests with cephalosporins. Five patients had positive skin tests with CE (Table 3). An oral challenge test with CE was performed in the first patient in whom the intradermal skin test with CE was positive to assess the value of this skin test. A generalized urticaria was elicited with a dose of 500 mg. No challenge test was performed in the other patients with positive skin test because the symptoms elicited by penicillins had been more severe. Four of the five patients positive to CE had positive skin tests with AMP/AX, the fifth having a positive RAST to AX and AMP.

Skin tests with CEF were negative in all the patients tested. Twenty-nine out of 34 patients diagnosed as allergic to penicillin and with negative skin test to CE tolerated this drug, and 30 patients were skin test negative to CEF, tolerating it up to therapeutic doses.

Table 1. Antibiotics and highest concentrations used in intracutaneous skin tests

Drugs	Conc. (mg/ml)
Amoxicillin (Beecham Pharmaceuticals, London, UK)	10
Ampicillin (Beecham Pharmaceuticals, London, UK)	10
PPL (Allergopharma JGKG, Hamburg, Germany)	5×10^{-5} M
MDM (Allergopharma JGKG, Hamburg, Germany)	1×10^{-2} M
Cephalexin (Almirall SA, Barcelona, Spain)	2.5
Ceftazidime (Glaxo-Allen, Madrid, Spain)	2.5

Table 2. Clinical data of cases studied

Pat. no.	Sex	Age (yr)	Drug	No. of reactions	Clinical manifestation
1	F	60	BP, AX	4	Anaphylactic shock
2	M	48	AM	1	Generalized maculopapular rash, angioedema, and breathing difficulties
3	F	40	BP	1	Generalized maculopapular rash
4	F	52	BP	1	Hypotension and generalized erythema
5	M	47	?	2	Generalized maculopapular rash, pruritus, and angioedema
6	F	38	BP	3	Generalized pruritus and maculopapular rash
7	M	37	AX	1	Generalized maculopapular rash and dysphagia
8	M	36	AM	1	Generalized pruritus and erythema
9	M	46	BP	1	Generalized maculopapular rash and angioedema
10	F	27	AX	1	Generalized maculopapular rash and facial angioedema
11	M	55	AX	2	Generalized pruritus and maculopapular rash
12	M	37	BP	1	Generalized pruritus and maculopapular rash
13	F	30	AX	2	Anaphylactic shock
14	M	34	AM	1	Generalized erythema, pruritus, and breathing difficulties
15	F	12	AX	1	Anaphylactic shock
16	F	19	AX	1	Anaphylactic shock
17	F	39	AX	2	Generalized pruritus, maculopapular rash, and facial angioedema
18	F	63	AOX	2	Generalized pruritus and erythema
19	M	53	BPO, AX	2	Generalized pruritus and maculopapular rash
20	F	35	AX	2	Anaphylactic shock
21	M	36	AX	1	Maculopapular rash and facial angioedema
22	M	29	AM	1	Generalized pruritus, dysphonia, dysphagia, and breathing difficulties
23	M	69	AM	1	Generalized pruritus, maculopapular rash, facial angioedema, and vomiting
24	F	45	AX	1	Anaphylactic shock
25	F	19	AX	1	Generalized maculopapular rash
26	M	40	AX	2	Generalized maculopapular rash and facial angioedema
27	F	48	AX	1	Generalized maculopapular rash
28	F	32	AX + CLAV	1	Pruritus, generalized maculopapular rash, and dysphagia
29	F	44	AX	1	Anaphylactic shock
30	F	72	BP	1	Anaphylactic shock
31	F	66	AX	1	Generalized pruritus and maculopapular rash
32	M	34	AM	1	Generalized maculopapular rash
33	M	57	AM	1	Generalized maculopapular rash
34	M	42	AX	2	Generalized pruritus and erythema

Discussion

Penicillins are the group of antibacterial agents most frequently involved in allergic reactions to drugs (9, 21). The widely used reagents for *in vivo* diagnosis of immediate reactions are major and minor determinants of benzylpenicillin (BPO-PLL and MDM), and the *in vitro* test is the quantification of specific IgE to BPO. Levine & Zolov reported that the presence of a negative skin test in a suspected case of allergy to penicillin with these determinants excludes the possibility of an immediate or accelerated allergic reaction (13). In the data presented in Levine & Zolov's study, different semisynthetic penicillins were used in addition to benzylpenicillin, and in no case was a positive skin test detected while negative to the reagents derived from benzylpenicillin (13). Similar results have been reported by others (9). However, early experimental and clinical data have indicated a heterogeneity in the production of both IgG and IgE antibodies to the chemical structure of penicillin (5, 17). Solley et al. later found a

selective response to some semisynthetic penicillins, the number of skin-test-positive reactors increasing (20). Others have reported similar results (4, 7, 18). These differences can be related to the pattern of consumption of penicillins. Recently available data indicate that in a large group of allergic patients in whom 50% of the consumption was related to AX, 31% of the patients studied proved to be positive to AX by either skin test, RAST, or challenge, but with good tolerance of benzylpenicillin (7).

Of the total number of positive skin tests in our study, AX or AMP was positive in 76%, and BPO or MDM in 64%. Although the total reactivity to BPO or MDM was 47%, when only the cases positive to AX or AMP were considered, it was 26%. These figures are higher than previously reported (7, 18). Blanca et al. reported a 12.55% positivity to AX in a large group of patients allergic to various penicillins (7), and Silviu-Dan et al. found that in a group of 228 cases evaluated for allergy to penicillins, 15% of all the positive reactors were positive only to AMP (18).

Table 3. Results obtained by skin tests and RAST

Pat. no.	Skin tests						RAST			Challenge		
	PPL	MDM	AMP	AX	CE	CEF	BPO	AMP	AX	AX	CE	CEF
1	+	+	-	-	-	-	23	-	-	nt	-	-
2	-	-	+	-	-	-	-	-	-	nt	-	-
3	-	-	+	+	-	-	-	-	-	nt	-	-
4	-	-	-	-	-	-	4	-	-	nt	-	-
5	+	+	+	+	+	-	46	17	6	nt	nt	nt
6	+	-	-	-	+	-	3.5	6.5	6.7	nt	nt	nt
7	-	-	-	+	-	-	-	-	-	nt	-	-
8	-	-	+	+	+	-	-	-	-	nt	+	-
9	+	-	-	-	-	-	8	2.4	2	nt	-	-
10	-	-	-	+	-	-	-	-	-	nt	-	-
11	-	-	-	-	-	-	-	-	-	+	-	-
12	+	-	-	-	-	-	13.5	3.6	-	nt	-	-
13	+	-	+	+	+	-	-	-	-	nt	nt	nt
14	+	+	-	-	-	-	26	41	19	nt	-	-
15	-	-	-	-	-	-	5	-	-	nt	-	-
16	-	-	+	+	-	-	-	11	-	nt	-	-
17	-	-	-	-	-	-	-	-	-	+	-	-
18	-	-	-	-	-	-	-	-	-	+	-	-
19	-	-	+	+	-	-	-	-	-	nt	-	-
20	-	+	-	+	-	-	-	-	-	nt	-	-
21	-	-	-	-	-	-	-	-	-	+	-	-
22	-	+	+	-	-	-	-	-	-	nt	-	-
23	+	+	+	+	+	-	45	4	4	nt	nt	nt
24	-	+	+	+	-	-	-	-	-	nt	-	-
25	-	-	+	-	-	-	-	10	-	nt	-	-
26	-	-	-	-	-	-	-	4	3	nt	-	-
27	-	-	-	-	-	-	-	-	-	+	-	-
28	-	+	+	+	-	-	-	-	-	nt	-	-
29	-	-	+	+	-	-	-	-	-	nt	-	-
30	+	+	+	-	-	-	16	-	-	nt	-	-
31	-	+	+	-	-	-	-	-	-	nt	-	-
32	+	-	+	+	-	-	-	-	-	nt	-	-
33	+	+	-	-	-	-	20	-	-	nt	-	-
34	-	-	-	-	-	-	-	-	-	+	-	-

PPL, BPO-polylysine; BPO, benzyl-penicilloyl; MDM, minor-determinant mixture; AMP, ampicillin; AX, amoxicillin; CE, cephalixin; CEF, ceftazidime; nt, not tested.

Skin tests positive: wheal diameter 4 mm greater than initial bleb in two perpendicular directions and erythema. PBO, AM, and AX-RAST results expressed in proportion conjugated counts/HSA counts (negative under 2).

Although skin testing with minor and major determinants of benzylpenicillin is the method generally used for diagnosis (3, 9) and seems to be more sensitive than the *in vitro* test for detecting IgE antibodies (15, 22), we have found cases of positivity to *in vitro* conjugates of BP, AX, and AMP-HSA only. Similar results have been reported by others (12).

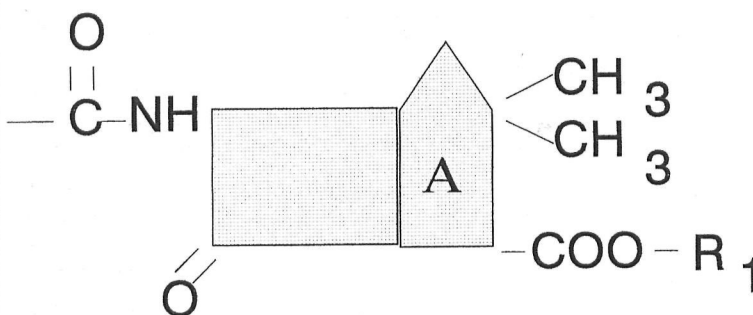
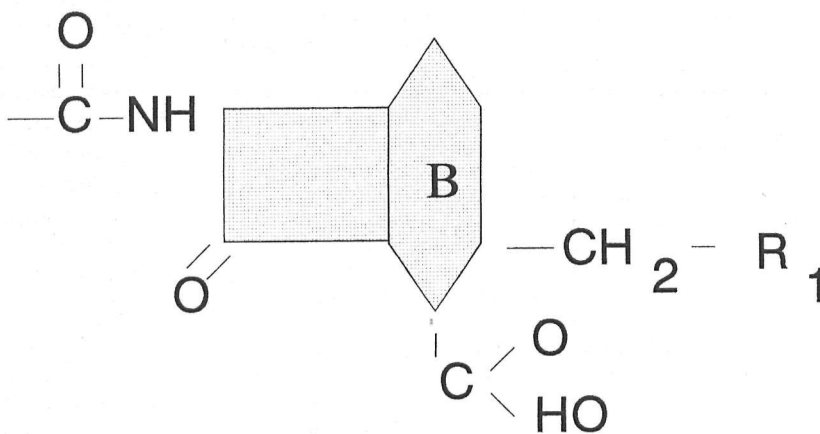
The addition of AX and AMP to the conventional penicillin determinants permitted diagnosis of nine patients (26%) who would not have been diagnosed if a challenge test had been performed. Hence, the tests with AX/AMP improved the diagnosis in 26% of patients in our study. This contrasts with previously reported cases (13, 20) indicating that a low reactivity rate existed after the administration of penicillin in patients with negative skin tests. This

result has been confirmed recently by Sogn et al. (19). The most striking difference between their study and ours is that they did not include AX and AMP in skin testing and challenging. Since these penicillin derivatives were not included, results could not be compared. However, AMP and AX are frequently used drugs in the USA. According to data provided by the Computerized On-line Medicaid Pharmaceutical Analysis and Surveillance System (CAM-PASS), AX and AMP were the most common drugs used in the population surveyed (8). Thus, if we followed the same approach made by others (6, 7), these drugs should have been used in this study.

Although the betalactams involved in the induction of allergic reactions could be different in the population studied, MDM of AX and AMP, in addition to BPO and MDM of benzylpenicillin, were used in one of these studies. Since, in most of our cases, the offending drug was AX, and an important proportion of patients proved to be positive by skin testing to AX and/or AMP, we considered studying the cross-reactivity with an aminocephalosporin, CE, and with a rather different third-generation compound, CEF. Although some reports (3) have established that intradermal skin tests with cephalosporins at concentrations higher than 1 mg/ml are irritant, in our study we have not found false positive results with the CE and CEF concentrations shown above (up to 2.5 mg/ml). Five patients had a positive skin test with AMP/AX.

The clinical relevance of the side chain (Fig. 1) in penicillin allergy has recently been reported by Blanca et al., who described cases of sensitization exclusively to AX with good tolerance of BP (7). The influence of the side chain in producing common antigenic determinants in penicillins and cephalosporins has been studied *in vitro* (6) and also in experimental studies (5, 10). The side chain is more relevant in cephalosporin antigenicity since the metabolic products equivalent to the penicilloyl groups are very unstable, and cephalosporin degradation products similar to penicillin minor determinants have not been identified (11). Specific antibodies against the side chain have been demonstrated in animal studies (11, 14, 16). There is cross-reactivity among BPO antibodies and some first-generation cephalosporins, but this reactivity is quite different from that of the benzylpenicillin side chain (5).

When antibodies against BP are directed primarily to the acyl side chain, they cross-react with the thiopene side chain cephalotin but only to a minor degree with the aminophenyl side chain of CE. Cephaloran, a cephalosporin with a side chain identical to that of benzylpenicillin, shows a strong cross-reactivity (11). Furthermore, Adkinson et al. have reported that in rabbit-raised IgG antibodies a monobactam with a side chain similar to that of



main.

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