

Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin

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In recent years, patients allergic to amoxicillin (AX) but with good tolerance of penicillin G (PG) have been described. It has been suggested that the epitope implicated in this type of sensitization might be located on the side-chain of the AX molecule. Thus, cross-reactivity between AX and cephadroxil (CEPH), a cephalosporin which shares an identical side-chain with AX, is suspected. This study aimed to demonstrate clinical cross-reactivity between AX and CEPH in patients allergic to AX and showing good tolerance of PG. In 76 of 576 subjects with suspected allergic reaction to PG and/or AX, the diagnosis of allergy was confirmed. All of these had specific IgE to PG, penicillin V, or AX, and/or positive skin tests to PPL (penicilloyl-polylysine), or MDM (minor determinant mixture), or PG, or AX, and/or positive challenge tests with PG and/or AX. Sixteen subjects (21%) allergic to AX (11 with positive skin test and five with positive challenge test to AX) and good tolerance of PG (all with negative parenteral challenge test) were selected. These 16 patients were subsequently challenged with CEPH (up to 500 mg). Fourteen patients tolerated CEPH, and two (12%) had an immediate allergic reaction. Our study indicates that allergy to the side-chain of aminopenicillins seems to have little clinical relevance in patients with allergic reactions to aminopenicillins but with good tolerance of PG, as 88% of patients with this clinical characteristic tolerate a cephalosporin which shares an identical side-chain. It seems that IgE from most of these patients recognizes an epitope different from the side-chain and the β -lactam ring.

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In previous studies, patients with immediate allergic reactions to amoxicillin (AX) but with good tolerance of penicillin G (PG) have been described (1–3). This reaction has been attributed to specific sensitization to the side-chain, since AX differs from PG only in the side-chain, in which AX contains additional α -amino and *p*-hydroxy groups. However, this hypothesis has not been totally confirmed by *in vivo* or *in vitro* studies.

In this paper, we present a group of patients who experienced immediate reactions to β -lactams, including a subgroup, with allergic reaction to AX, but with good tolerance of PG. Within this subgroup of patients, we also analyze the oral tolerance

of cephadroxil (CEPH), a cephalosporin with a side-chain identical to that of AX (Fig. 1).

Material and methods

Patients

Between December 1992 and March 1995, a total of 576 patients were referred to our outpatient clinic with suspected allergic reaction to penicillin or its derivatives. According to clinical history, AX was involved in 252 patients and benzylpenicillin in 147 patients; in 177 patients, we were unable to identify the antibiotic involved. All patients received

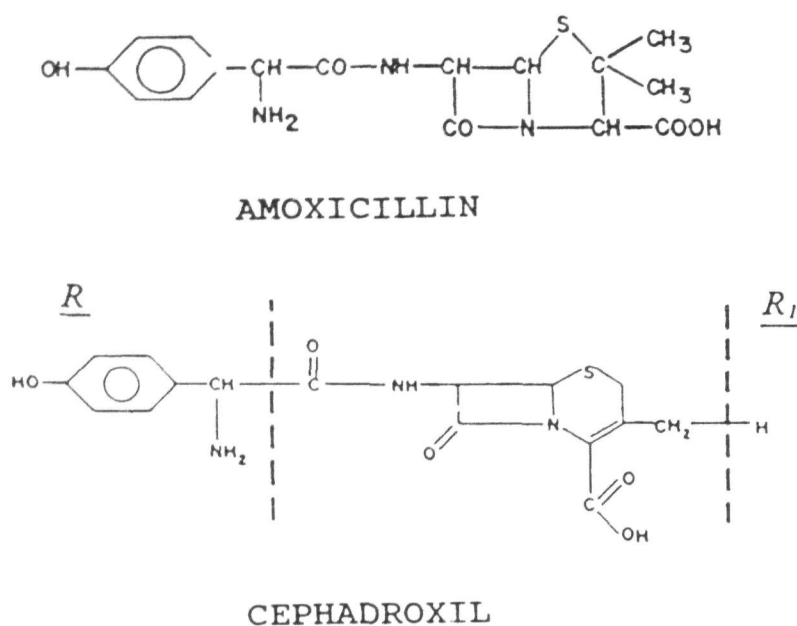


Fig. 1. Structures of amoxicillin and cephadroxil.

information about the possible risks of skin and challenge tests, and before admission to the study, written, informed consent was given by all patients or their guardians.

In vitro tests

Specific IgE to PG and AX was determined in serum by the CAP System (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions, and results of >0.35 kU/l were considered positive.

Skin tests

Reagents. The following reagents were used for the skin tests. Penicilloyl-polylysine (PPL) 5×10^{-5} M and minor determinant mixture (MDM) 1×10^{-2} M were obtained from Allergopharma JGKG (Hamburg, Germany). Benzylpenicillin (penicillin G) sodium salt (Antibiotic Farma SA, Madrid, Spain) was diluted in saline solution (Braun Medical SA, Barcelona, Spain) until reaching a concentration of 10 000 UI/ml. Sodium amoxicillin (Beecham Pharmaceuticals, London, UK) was applied in a concentration of 25 mg/ml in saline. These concentrations had previously been shown to be nonirritant in a group of 50 subjects with no history of PG sensitivity. Histamine HCl 10 mg/ml (A. I. Abelló, Madrid, Spain) and glycerosaline or saline (A. I. Abelló, Madrid, Spain) were used as controls.

Procedures for skin and challenge tests

All 576 patients were skin tested on the forearm by prick testing with PPL, MDM, PG, and AX. A wheal 3 mm greater than that of glycerosaline with a surrounding area of erythema was considered positive. If the prick tests were negative, a minimal

amount (0.01–0.03 ml) of the testing material was injected intradermally. A wheal 5 mm greater than the control with a surrounding area of erythema was considered positive. If the intradermal skin test with PPL, MDM, and PG was negative, PG was administered intramuscularly, beginning with 1000 U and increasing progressively to as much as 1 200 000 U. After completing the dose of PG, the patient was requested to return 20 days later to be skin-tested and challenged with PG in a manner identical with the initial evaluation (rechallenge).

Oral AX was administered in progressively increasing doses from 25 to 500 mg every 45 min unless a reaction occurred. Patients considered to be specifically allergic to AX with good tolerance of PG were challenged with oral CEPH in a manner identical to the AX challenge tests. During this period, the patients were carefully monitored for symptoms compatible with an IgE-mediated allergic reaction. All challenge tests were carried out in a single-blind fashion. Complete equipment for cardiopulmonary resuscitation is always available in our clinic.

Results

Seventy-six of 576 (13.1%) patients studied were diagnosed as having allergy to penicillin and/or AX. Of these 76 patients, 38 (50%) had a positive skin test to one or more of the penicillin skin test materials (PPL, MDM, or PG), 22 (28.9%) to at least one penicillin determinant and AX, and 11 (14.4%) to AX exclusively. All patients with negative skin tests to PPL, MDM, or PG had negative challenge tests with PG. Sixteen (21%) patients were allergic only to AX, but with good tolerance of penicillin. The clinical characteristics of these 16 patients are summarized in Table 1. The results of skin, specific IgE, and challenge tests are shown in Table 2. All but one patient in this group had not been previously treated with PG. Eleven (68%) patients had positive skin tests to AX, four by prick, and seven by intradermal test. None of these patients experienced systemic reaction to AX skin tests. Seven patients, five of whom had negative skin tests to AX, were challenged with AX, and all developed skin reactions within the first hour of oral AX administration (Table 3). In two cases, we decided to challenge in spite of positive skin test to AX, due to an uncertain history of reaction to AX. All patients required treatment. Sixteen patients allergic solely to AX were challenged with oral CEPH, and only two (12%) developed urticaria and generalized pruritus within the first hour of administration of 250 and 500 mg, respectively.

Table 1. Clinical characteristics of patients allergic to amoxicillin (AX) and with good tolerance of penicillin

Patient no.	Sex	Age (years)	Drug	No. of reactions	Clinical reaction	Time (months)
1	M	41	AX	2	GP, urticaria	12
2	F	15	AX	2	GP, urticaria, angioedema	10
3	F	24	AX	1	GP, urticaria, angioedema	2
4	F	38	AX	1	GP, urticaria	5
5	M	43	AX	2	GP, urticaria, dysphagia	8
6	M	42	AX	1	GP, maculopapular rash	5
7	F	49	AX	2	GP, maculopapular rash	7
8	M	39	AX	2	GP and facial angioedema	8
9	F	3	AX	1	GP, urticaria	15
10	F	37	AX	1	Urticaria, facial angioedema	12
11	M	42	AX	2	GP, maculopapular rash	1
12	M	45	AX	1	GP, urticaria	2
13	F	31	AX	3	Urticaria, vomiting	1
14	F	40	AX	2	Urticaria, facial angioedema	10
15	M	20	AX	2	Generalized urticaria	6
16	M	23	AX	1	Generalized urticaria	1

Time: months elapsed since last historical allergic reaction to AX and skin and challenge tests.

GP: generalized pruritus.

Table 2. Results of skin, specific IgE, and challenge tests in patients allergic to amoxicillin but with good tolerance of penicillin

Patient no.	CAP		Skin tests		Challenge tests		
	PG	AX	PG*	AX	PG	AX	CEPH
1	—	—	—	—	—	+	+
2	—	—	—	+ ^I	—	+	—
3	—	—	—	+ ^I	—	NT	—
4	—	—	—	+ ^I	—	NT	—
5	—	+	—	+ ^P	—	NT	+
6	—	—	—	—	—	+	—
7	—	—	—	+ ^I	—	NT	—
8	—	—	—	—	—	+	—
9	—	—	—	—	—	+	—
10	—	—	—	+ ^P	—	NT	—
11	—	—	—	+ ^P	—	NT	—
12	—	—	—	+ ^I	—	NT	—
13	—	—	—	+ ^I	—	NT	—
14	—	—	—	+ ^I	—	+	—
15	—	—	—	+ ^P	—	NT	—
16	—	—	—	—	—	+	—

PG: penicillin G, AX: amoxicillin, CEPH: cephadroxil, NT: not tested.

—: negative test, +: positive test.

*: PPL, MDM, PG reagents.

P: prick.

I: intradermal.

Discussion

The pattern of allergic reaction to β -lactams is changing, as is also the consumption of different penicillins. In Spain, for example, during 1994, the consumption of PG was 1 311 300 units, while that of semisynthetic penicillins was 268 551 000 units, AX comprising 95% of these (4). In the USA, ampicillin and AX are also frequently used (5). At the present time, many subjects have been exposed only to semisynthetic penicillins, and never to PG. In fact, only one of the 16 patients allergic solely to AX had been previously treated with PG. Therefore, we expect an increase in allergic reactions involving only AX. Although it has become clear that the drug-specific immune response is directed largely toward the nuclear structure which is common to all semisynthetic penicillins, in other cases the immune response may be directed toward other structures of the molecule. In 1988, Blanca et al. (1) first described patients allergic to AX, but with good tolerance of PG. Some experimental and clinical data suggest that antibodies in these patients can be produced by immunogenic epitopes on the side-chain (1, 2, 6, 7). The same group (3) has

Table 3. Challenge tests with oral amoxicillin

Patient no.	Dose (mg)	Reaction	Onset of reaction after challenge (min)
1	25	Generalized erythema and GP	50
2	125	Facial erythema and GP	45
6	25	Arm and leg exanthema and GP	30
8	25	Arm and leg exanthema and GP	20
9	50	Exanthema and GP	45
14	500	Exanthema and angioedema, GP	60
16	25	Generalized urticaria	15

GP: generalized pruritus.

recently presented a larger experiment with subjects allergic to AX. They reported that 54/177 (30.5%) patients allergic to β -lactams were allergic to AX, but with good tolerance of PG.

In our group of patients, this percentage was slightly lower – 21% – but this difference was not statistically significant. Skin tests with AX were positive in 68% of patients allergic only to AX, a figure similar to that reported by Vega et al. (3). These results emphasize the need to include aminopenicillin reagents in the skin test routine for the diagnosis of β -lactam allergy, since they had negative skin tests to AX (8, 9). However, five cases (31%) in our study required a challenge test in order to establish a definitive diagnosis. This figure is also similar to that reported by Vega et al. (3). Only 1/16 (6%) sera from patients allergic only to AX was positive for specific IgE to AX by the CAP System; in all cases, specific IgE to PG was negative. Thus, we can conclude that AX-CAP does not appear to be useful for the diagnosis of patients allergic only to AX. This contrasts with the 44% of positive RAST to AX detected in the group of patients described by Vega et al. (3). Nevertheless, the technique used by them is different from that which is commercially available.

The main aim of this study was to detect clinical cross-reactivity between AX and CEPH, a cephalosporin with a side-chain identical with that of AX, in the group of patients allergic to AX, and with good tolerance of PG. Surprisingly, only 2/16 patients (12%) showed an immediate reaction to CEPH. Audicana et al. (10) have recently evaluated the cross-reactivity among allergic patients to penicillins and to some cephalosporins. In this study, they challenged patients with cephalexin, a cephalosporin with a side-chain identical with that of ampicillin. In 10 patients with positive skin test to ampicillin, but with negative skin test to PPL or MDM of penicillin, only one patient had a positive skin test and challenge test to cephalexin (10%), while all the others tolerated oral cephalexin. Thus, the incidence of cross-reactivity in our study is similar to that reported with another aminopenicillin and a cephalosporin with an identical side-chain, and similar as well to the general cross-reactivity between penicillins and cephalosporins with an unrelated side-chain (11–14).

In conclusion, our study indicates that allergy to the side-chain of aminopenicillins seems to have

little clinical relevance in patients with allergic reactions to aminopenicillins, but with good tolerance of PG, as 88% of patients with this clinical characteristic tolerated a cephalosporin which shares an identical side-chain. Further studies are necessary to determine the epitope(s) causing sensitization in these patients.

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