

Immediate allergic reactions to cephalosporins: Evaluation of cross-reactivity with a panel of penicillins and cephalosporins

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Background: Allergy to cephalosporins has mainly been evaluated in the context of patients with confirmed penicillin allergy. The problem of studying cross-reactivity in subjects primarily sensitized to cephalosporins and potentially allergic to penicillins has not been sufficiently addressed.

Objective: To evaluate the *in vitro* IgE response and cross-reactivity to betalactams in patients with immediate allergic reactions to cephalosporins.

Methods: The study included 24 patients with immediate allergic reactions to cephalosporins and RAST-positive to at least 1 cephalosporin. Skin testing and RAST were performed with a panel of penicillins and cephalosporins. RAST inhibition assay with different monomeric conjugates of penicillin and cephalosporin was performed to establish cross-reactivity. **Results:** The culprit cephalosporins were cefaclor (N = 7), cefonicid (N = 1), cefotaxime (N = 2), ceftazidime (N = 2), ceftriaxone (N = 3), and cefuroxime (N = 9). Two patients had a positive skin test result to penicillin determinants, and 22 patients had a negative result to penicillin determinants and tolerated benzylpenicillin administration. Of these 22, 19 had a positive skin test result to cephalosporins and divided into patients reacting only to the culprit cephalosporin (63.2%) and those reacting to more than 1 cephalosporin (36.8%). RAST and RAST inhibition studies confirmed that the side chain at the R1 position is crucial for recognition.

Conclusion: The R1 side chain rather than the betalactam structure, shared by penicillins and cephalosporins, seems to play a dominant role in determining the specificity of immunologic reactions to cephalosporins. Thus, penicillin can be administered safely to patients allergic to cephalosporins and with a negative skin test result to penicillin determinants. (J Allergy Clin Immunol 2006;117:404-10.)

Key words: IgE, cephalosporin, penicillin, allergic reactions, cross-reactivity

The increased therapeutic use of cephalosporins and the appearance of selective allergic responses to these

Abbreviation used

PLL: Poly-L-Lysine

compounds are causing concern.¹ The number of publications regarding allergic reactions to cephalosporins is growing, although most studies are mainly case reports, or series with limited numbers of patients.²⁻⁶ Evidence so far available suggests that differences exist in the percentage of patients who have an immediate allergic reaction to cephalosporins in case series^{7,8} and within the same population when the study is performed at different times.^{5,6} In severe allergic reactions to antibiotics, cephalosporins have been shown to be the responsible drug in a relatively important percentage of cases (as much as 15%).⁹

In the past, allergy to cephalosporins was considered in the context of penicillin allergy, and the question involved was assessment of tolerance in patients primarily sensitized to penicillin derivatives.¹⁰⁻¹⁴ However, the problem of studying cross-reactivity in subjects primarily sensitized to cephalosporins and potentially allergic to penicillins has not been sufficiently addressed.

Cephalosporins form a large group of compounds with important differences in their chemical structure and behavior. Both the R1 and the R2 side chains may contribute to the configuration of different epitopes, although this has not yet been properly demonstrated.¹⁵ After the opening of the betalactam ring by the amino group of the carrier, the R2 side chain disappears, and a heterogeneous fragmentation of the cephalosporin occurs. Hence, the final product of the epitope is formed by the remaining betalactam and the R1 side chain.¹⁶ A schematic representation of the opening of the betalactam ring by butylamine (ⁿBuNH₂) is shown in Fig 1.

In this work, we evaluated a group of subjects who, after having had an immediate allergic reaction to a cephalosporin within the previous 4 years, had detectable specific IgE antibodies in sera to at least the compound involved in the reaction. Skin testing and *in vitro* analysis, using RAST and RAST inhibition assays with a panel of different betalactam compounds, including 3 penicillins and 6 cephalosporins, were performed to assess the pattern of the skin test response, the specificity, and the cross-reactivity.

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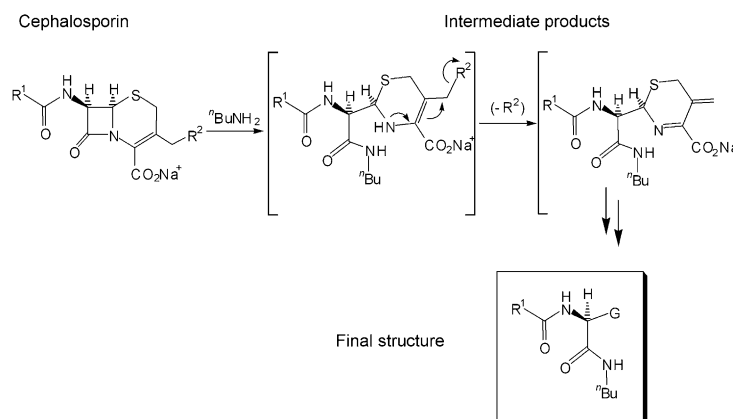


FIG 1. Metabolic transformation of the original cephalosporin molecule by the opening of the betalactam ring by an amino group of butylamine.

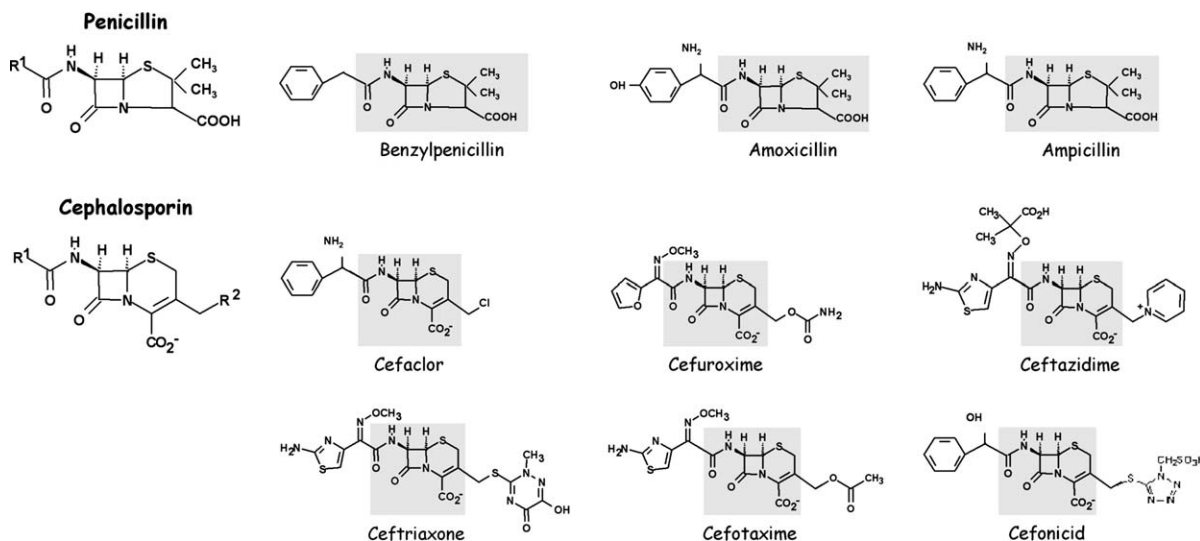


FIG 2. General chemical structures of penicillin and cephalosporin molecules and chemical structures of the different betalactams used in this study.

METHODS

Patients

Over a 4-year period (2000-2004), we studied a group of patients with immediate allergic reactions to cephalosporins, according to the European Network for Drug Allergy protocol.¹⁷ Briefly, the evaluation consisted of a skin test and determination of specific IgE antibodies, by RAST, to a panel of different betalactams, including the culprit drug (Fig 2). Only those patients with RAST positive to at least 1 cephalosporin were finally included in the study. Two clinical categories were established: anaphylaxis or urticaria.¹⁸

To confirm cephalosporin selectivity in those patients with skin test and RAST-negative to all of the penicillin derivatives tested, benzylpenicillin was administered to assess tolerance, as described.^{17,19}

The study was approved by the institutional review board, and informed consent for all of the diagnostic procedures was obtained from all patients.

Skin test

Skin testing was performed^{17,18} by using 0.02 mL solution prepared daily. The reagents and maximum concentrations accepted were benzylpenicilloyl-poly-L-lysine (5×10^{-5} M; Allergopharma Merck, Reinberck, Germany), minor determinant mixture (2×10^{-2} M; Allergopharma Merck), benzylpenicillin (10^5 IU/mL; Normon SA, Madrid, Spain), amoxicillin (20 mg/mL; SB Smithkline Beecham, Madrid, Spain), and ampicillin (20 mg/mL; Normon SA), and the following cephalosporins (2 mg/mL): cefaclor (Lilly, Madrid, Spain), cefuroxime (GlaxoSmithKline SA, Madrid, Spain), ceftazidime (GlaxoSmithKline SA), ceftriaxone (Roche, Basel, Switzerland), cefotaxime (Roussel Iberica Laboratorios, Madrid, Spain), and cefonicid (GlaxoSmithKline SA). Higher concentrations may cause nonspecific irritative reactions, even in subjects with good tolerance or no exposure to betalactams.¹⁷ In the skin prick tests, a wheal >2 mm was considered positive. In the intradermal tests, the wheal area was marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm was considered positive.^{17,18}

TABLE I. Clinical characteristics and skin test results with different haptens

Case	Age, y	Sex	Reaction	Drug	INT	Skin tests										
						PPL	MDM	BP	AX	AMP	Cefaclor	Cefuroxime	Ceftazidime	Ceftriaxone	Cefotaxime	Cefonicid
1	37	F	Anaphylaxis	Cefaclor	8	-	-	-	-	-	+	-	-	-	-	-
2	43	F	Urticaria	Cefaclor	5	-	-	-	-	-	+	-	-	-	-	-
3	16	F	Urticaria	Cefaclor	16	-	-	-	-	-	+	-	-	-	-	-
4	43	F	Anaphylaxis	Cefaclor	12	-	-	-	-	-	+	-	-	-	-	-
5	6	F	Anaphylaxis	Cefaclor	8	-	-	-	-	-	+	-	-	-	-	-
6	35	F	Anaphylaxis	Cefaclor	5	-	-	-	-	-	+	+	-	-	-	-
7	48	M	Urticaria	Cefaclor	15	-	-	-	-	-	+	-	-	-	-	-
8	52	F	Anaphylaxis	Cefonicid	21	-	-	-	-	-	-	-	-	-	-	-
9	21	F	Anaphylaxis	Cefotaxime	24	-	-	-	-	-	-	+	-	+	+	-
10	38	M	Urticaria	Cefotaxime	10	-	-	-	-	-	-	+	-	+	+	-
11	57	F	Anaphylaxis	Ceftazidime	120	-	-	-	-	-	-	-	+	-	-	-
12	44	M	Anaphylaxis	Ceftazidime	18	-	-	-	-	-	-	-	-	-	-	-
13	25	F	Anaphylaxis	Ceftriaxone	9	-	-	-	-	-	-	-	-	+	-	-
14	58	M	Anaphylaxis	Ceftriaxone	4	-	-	+	+	-	-	-	+	+	+	-
15	39	F	Urticaria	Ceftriaxone	12	-	-	-	-	-	-	+	-	+	+	-
16	47	M	Anaphylaxis	Cefuroxime	0.5	-	-	-	-	-	-	+	-	-	-	-
17	38	F	Anaphylaxis	Cefuroxime	3	-	-	-	-	-	-	+	-	-	-	-
18	42	F	Anaphylaxis	Cefuroxime	0.5	-	-	-	-	-	-	+	-	-	+	-
19	22	F	Anaphylaxis	Cefuroxime	0.5	-	-	-	-	-	-	+	-	-	-	-
20	36	F	Anaphylaxis	Cefuroxime	6	-	-	-	-	-	-	+	-	-	+	-
21	42	M	Anaphylaxis	Cefuroxime	1	-	-	-	-	-	-	+	-	-	-	-
22	53	M	Anaphylaxis	Cefuroxime	5	-	-	-	-	-	-	+	-	+	+	-
23	51	F	Urticaria	Cefuroxime	5	-	-	-	-	+	-	+	-	+	+	-
24	40	F	Anaphylaxis	Cefuroxime	0.5	-	-	-	-	-	-	-	-	-	-	-

AMP, Ampicillin; AX, amoxicillin; BP, benzylpenicillin; INT, interval reaction study (mo); MDM, minor determinant mixture; PPL, benzylpenicilloyl-poly-L-lysine.

*Skin test-positive by prick.

In vitro IgE determination

The *in vitro* IgE determination was made by RAST using benzylpenicillin, amoxicillin, ampicillin, cefaclor, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefonicid conjugated to Poly-L-Lysine (PLL; Sigma, St Louis, Mo) in the solid phase, as described.²⁰ Briefly, 30 μ L of the patient's sera was incubated in the solid phase with different betalactam-PLL conjugates. After washing, radiolabeled anti-IgE antibody (Pharmacia Diagnostics, Uppsala, Sweden) was added and incubated overnight. The discs were then washed, and their radioactivity was measured in a γ -counter, Cobra II autogamma (Packard BioScience Co, Frankfurt, Germany). Results were calculated as a percentage of the maximum and considered positive if they were higher than 2.5%, which was the mean + 2 SD of a negative control group.²⁰

In vitro determination of IgE specificity and cross-reactivity

In vitro determination of IgE specificity and cross-reactivity was performed by RAST inhibition assay with different betalactam, using in the solid phase the culprit cephalosporin conjugated to PLL, as described.²¹ Sera from those patients who had RAST values higher than 7% were incubated with different betalactam conjugated to butylamine in two 10-fold decreasing concentrations (100 mM and 10 mM) for 18 hours at room temperature. After this, the corresponding solid phase disc was added, and the RAST procedure was continued as described. The results were expressed as percentage inhibition with respect to the noninhibited serum. Comparison of the inhibition capacity of the monomeric conjugates was made at 50% inhibition.

RESULTS

We evaluated 127 patients with a history suggestive of immediate allergic reactions to cephalosporins. After the allergological work-up, 51 cases (40.1%) were finally confirmed as allergic: 39 (76.4%) were skin test-positive, 2 (5.9%) were skin test-negative and RAST-positive, and 9 (17.6%) skin test-negative and RAST-negative and therefore diagnosed by drug provocation test. The remaining 76 patients were skin test-negative and RAST-negative and also tolerated the culprit cephalosporin in a drug provocation test, and therefore were considered to be nonallergic. Comparing this group with the positive group, urticaria appeared in 70% of cases, whereas in the positive group, it appeared in 25% of cases. In this group, although temporal association and symptoms were compatible with an immediate reaction, the attributed cephalosporins were not the culprit drugs.

Of the 51 positive patients, 24 were RAST-positive (21 from the skin test-positive group and the 3 who were skin test-negative). Seven were men and 17 women, with a mean age of 38.9 years (range, 6-58 years). The culprit cephalosporin was cefaclor in 7 patients, cefonicid in 1, cefotaxime in 2, ceftazidime in 2, ceftriaxone in 3, and cefuroxime in 9. The mean time interval between the reaction and the study was 13.4 months (Table I).

TABLE II. RAST results with the different haptens

Case	Drug	RAST								
		BP	AX	AMP	Cefaclor	Cefuroxime	Ceftazidime	Ceftriaxone	Cefotaxime	Cefonicid
1	Cefaclor	0	0	0.59	8.68	0.35	0.35	0.13	2.87	0.3
2	Cefaclor	1.3	0.03	1.26	2.98	1.14	0.15	0	0.44	0.41
3	Cefaclor	0.06	0	0.58	7.68	0.47	0.58	0.26	0.96	0.37
4	Cefaclor	0.01	0.15	1.33	2.64	0	0	0	0.02	0
5	Cefaclor	0.59	0	0.04	7.1	3.07	0	0	0.19	0.02
6	Cefaclor	1.86	0.84	0.5	5.41	3.66	0.55	0.01	2.37	0
7	Cefaclor	0	0	0	31.23	1.86	0	0	2.32	0
8	Cefonicid	0.01	0.07	0.47	0.1	0.74	0.13	0.64	0.87	2.9
9	Cefotaxime	0	0	0	0.07	0.74	0.16	0.82	2.73	0.34
10	Cefotaxime	0	0.04	0.02	1.03	4.4	0.25	18.04	19.75	0.49
11	Ceftazidime	0.03	0	0	0.83	1.32	24.6	2.97	3.09	0.43
12	Ceftazidime	0	0	0.26	0	0.39	2.63	0.37	0.78	0.11
13	Ceftriaxone	0.15	0.06	0.71	0.03	1.42	0.07	3.54	3.01	0.24
14	Ceftriaxone	0.71	0.04	0.5	0	1.86	0.31	28.87	20.7	0.29
15	Ceftriaxone	0.1	0	0	0.47	3.45	0	4.69	4.65	0.56
16	Cefuroxime	0.05	0.07	0	0	4.86	0.1	1.25	4.14	0.65
17	Cefuroxime	0	0	0.33	0	6.74	0	0.04	0.84	0
18	Cefuroxime	0.09	0.07	0.22	0.06	7.46	0.15	0.29	1.18	0.24
19	Cefuroxime	0.29	0.41	0.41	0	2.62	0.28	0	0.53	0
20	Cefuroxime	0	0	0	0.73	21.74	0.67	2.99	13.9	1.08
21	Cefuroxime	0.06	0.11	0.4	0	9.43	0	0.16	0.89	0.18
22	Cefuroxime	0	0	0	0.32	2.83	0.01	0.27	0.83	0.17
23	Cefuroxime	0.4	0.8	0.4	1.83	3.09	0.2	0.53	1.09	0.54
24	Cefuroxime	0.7	0.6	1	0	17.38	0	0	0.39	0

The shading indicates positive results.

AMP, Ampicillin; AX, amoxicillin; BP, benzylpenicillin.

Within the whole group, skin testing was positive to at least the culprit cephalosporin in 21 cases and negative in 3. Of these 21 patients, 2 were also skin test–positive to penicillin determinants; the other 19 were positive only to cephalosporins, with 12 reacting to the culprit cephalosporin (63.2%) and 7 to the culprit cephalosporin plus at least 1 other cephalosporin (36.8%). When the culprit drug was cefaclor, 6 cases were exclusively positive to this drug, and 1 was also positive to cefuroxime. The cefonicid case was skin test–negative, and all of the cefotaxime cases were positive to various cephalosporins. Only 1 of the 2 ceftazidime cases was skin test–positive, and just to this compound. Ceftriaxone had a variable pattern of skin test response, with 1 case positive only to this compound, 1 to several cephalosporins. The other, in addition to various cephalosporins, was also skin test–positive to benzylpenicillin and amoxicillin. For cefuroxime, 3 cases were positive to this drug only, 4 were also positive to other cephalosporins, 1 was positive to cephalosporins and ampicillin, and 1 was skin test–negative (Table I).

Analysis by RAST assay (Table II) showed that for cefaclor, just 2 cases had a positive response to other cephalosporins. The cefonicid case only recognized this structure. Of the 2 cases primarily allergic to cefotaxime, 1 was also positive to ceftriaxone and cefuroxime (which have a similar or identical R1 side chain; Fig 2). Of the 2 cases positive to ceftazidime, 1 was also positive to ceftriaxone and cefotaxime (which both have an identical

R1 side chain to ceftazidime). The 3 ceftriaxone cases were also positive to cefotaxime, with 1 positive to cefuroxime as well. In the 9 cefuroxime cases, 1 was also positive to cefotaxime and another to ceftriaxone and ceftazidime.

Only 2 cases responded to penicillin determinants: patients 14, to benzylpenicillin and amoxicillin, and 23, to ampicillin by skin testing (Table I), but no *in vitro* IgE antibodies to the penicillin derivatives used were detected. In all those cases skin test–negative and RAST–negative to penicillin determinants (N = 22), good tolerance to benzylpenicillin up to therapeutic doses was assessed by drug provocation tests. Of these 22, 19 were skin test–positive and RAST–positive to cephalosporins, and 3 were only RAST–positive.

To study specificity and cross-reactivity in more detail, RAST inhibition assays were performed. These involved 4 patients allergic to cefaclor, 1 to cefotaxime, 1 to ceftazidime, 1 to ceftriaxone, and 4 to cefuroxime (Fig 3). In all cases, the most potent inhibitor was the culprit cephalosporin, with a different degree of cross-reactivity with other cephalosporins and a good correlation with the RAST assay. In the cefaclor cases (1, 3, 5, and 7), the inhibition was almost exclusively found with the monomeric conjugate of cefaclor, with a variable degree of cross-reactivity with other compounds. In case 1, cefotaxime and ceftazidime reached values higher than 50% inhibition at the higher monomeric concentration. It is important to mention that ampicillin-butylamine, a penicillin

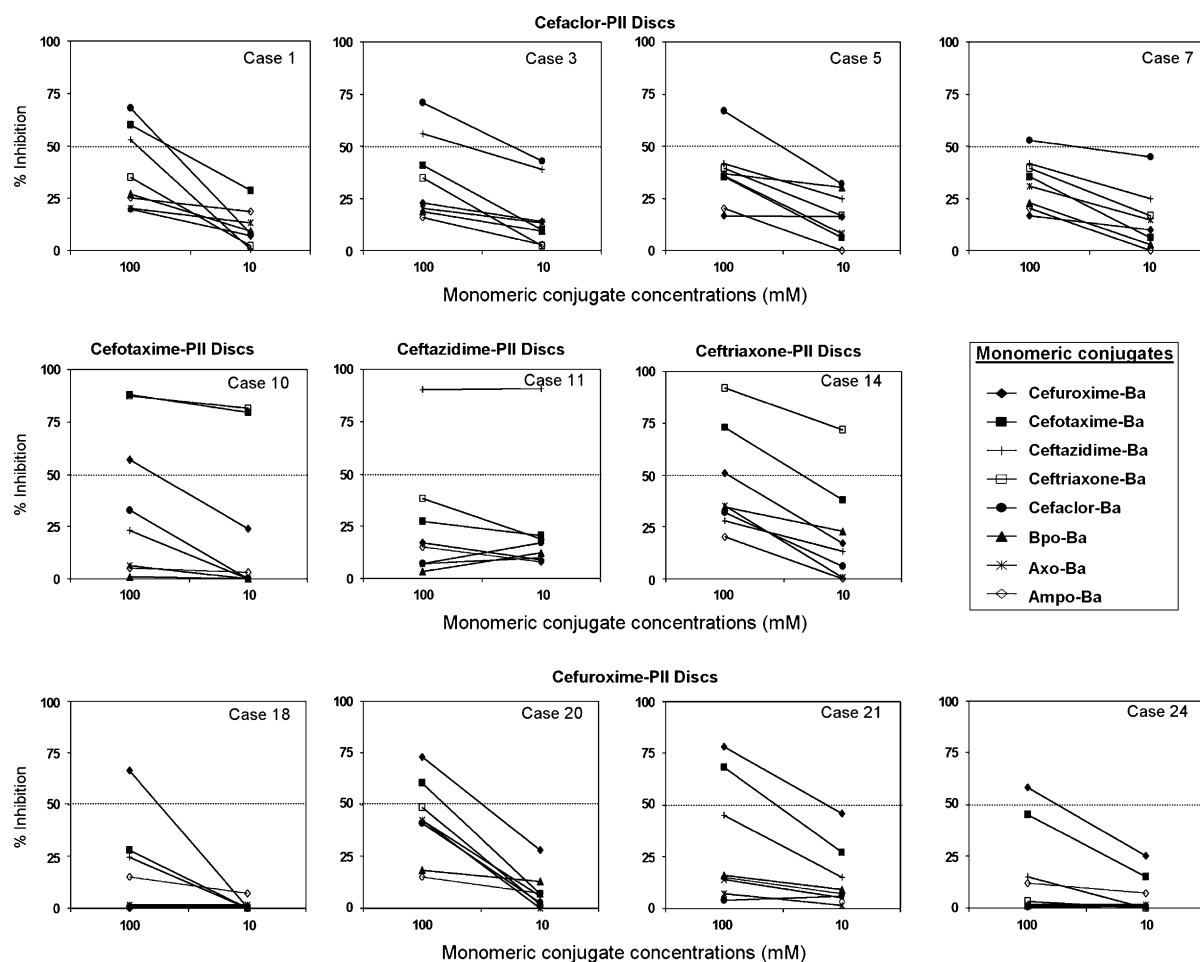


FIG 3. RAST inhibition assays of the different serum samples using discs bound to the culprit cephalosporin conjugated to PLL as the solid phase, and different betalactams conjugated to butylamine as the fluid phase.

with the same R1 side chain as cefaclor, was in all instances among the lowest inhibitors (<25% at 100 mmol/L). Case 10, a patient allergic to cefotaxime, was equally inhibited by cefotaxime and ceftriaxone, which have the same R1 side chain, and to a lesser extent by cefuroxime, which has a similar R1 side chain. Interestingly, this case was skin test-positive and RAST-positive to all 3 compounds. Case 11 responded to ceftazidime and had a very strong inhibition, even with just 10 mmol/L concentration of its monomeric conjugate, with no inhibition of the other conjugates (all below 50%). Case 14, initially positive to ceftriaxone, was also inhibited by another cephalosporin with the same R1 side chain (cefotaxime) and to a lesser extent by another cephalosporin with a similar side chain (ceftazidime). Interestingly, this case was skin test-positive to benzylpenicillin and amoxicillin, but no *in vitro* IgE recognition was detected by using RAST or RAST inhibition assays. For cefuroxime (cases 18, 20, 21, and 24), two patterns of response were detected, confirming the RAST results. In cases 20 and 21, cefotaxime, a cephalosporin with a similar R1 side chain to cefuroxime, was the strongest

inhibitor after cefuroxime, and in cases 18 and 24, only the monomeric conjugate of cefuroxime was above 50% inhibition at the 100 mmol/L concentration.

DISCUSSION

Although previous studies have estimated the frequency of immediate allergic reactions to cephalosporin to be rare,¹⁴ reports published since the 1990s indicate that the number of subjects primarily sensitized to cephalosporins is increasing.^{5,22} Recently, in a French Allergy Vigilance Network report of severe drug allergy, of all of the betalactams involved, 27% were cephalosporins.⁹ The evaluation of patients primarily allergic to cephalosporins has not been sufficiently addressed. General information concerning the response to different penicillins and cephalosporins is lacking.¹⁰⁻¹⁴ Allergic reactions to cephalosporins may occur because of sensitization to unique cephalosporin haptens or to determinants shared with penicillins,²³⁻²⁵ although the different epitopes have not been defined. The main objective of the current study was

to evaluate in a well-defined group of patients with immediate allergic reactions to cephalosporins the pattern of IgE recognition with other cephalosporins and penicillins. Thus, the criterion established was to have had an immediate allergic reaction to a cephalosporin and *in vitro* IgE positivity to at least 1 of the cephalosporins evaluated.

The skin test results showed that 19 (90.5%) patients were skin test-negative to penicillin determinants and tolerated benzylpenicillin up to therapeutic doses in a provocation test, and that only 2 patients (9.5%) were also positive to penicillin determinants. In a study performed in a group of Italian subjects with immediate allergic reactions to different cephalosporins, the percentage of cases that also recognized penicillin determinants was 5 times higher (50%).⁵ However, these differences were not observed in a similar study performed 5 years later in the same population.⁶ Because the approaches were similar in all 3 studies, it can be speculated that these differences were a result of the fact that most of the subjects in our study (undertaken from 2000 to 2004) and those in the 2000 Italian study⁶ had adverse reactions to second-generation and third-generation cephalosporins and none to first-generation cephalosporins, whereas some patients in the first Italian study⁵ had also reacted to first-generation cephalosporins, whose structural features are more similar to those of penicillin.

In our study, analysis of the skin test response in those patients who tolerated benzylpenicillin resulted in 2 groups: $\frac{2}{3}$ of the patients reacted only to the culprit cephalosporin (63.2%) and $\frac{1}{3}$ to at least 1 other cephalosporin as well as the culprit drug (36.8%). In this latter group, except for case 6, the cephalosporins involved shared the same R1 side chain. These results are similar to those of the Italian study evaluating patients with immediate allergic reactions to second-generation and third-generation cephalosporins, although in that study, the subgroup with cross-reactivity was higher (42.3%).⁶ Although no statistical comparisons can be made between these 2 groups, it is tempting to speculate that these differences could be a result of the different proportion of the culprit cephalosporins, with ceftriaxone and cefotaxime more common in the Italian population versus cefuroxime and cefaclor in our study. Ceftriaxone and cefotaxime are the cephalosporins with the highest degree of skin test cross-reactivity, probably because they share the same R1 side chain, whereas cefuroxime and cefaclor tend to induce more selective reactions.

Analysis of the *in vitro* specific IgE antibodies showed good agreement between the skin test and RAST results, although no patient who was skin test-positive to penicillin determinants had detectable specific IgE antibodies to penicillin determinants, because of the lower sensitivity of RAST.^{17,18}

Lack of knowledge of the exact chemical structure of cephalosporin antigenic determinants has hindered clinical interpretation of allergic reactions to these drugs and delayed understanding of the specific recognition and cross-reactivity. Many attempts have been made to understand this, such as the production of mAbs showing

that unique structures, formed by the R1 side chain plus part of the nuclear structure, were capable of inducing a specific immunologic response without cross-reacting with the classical penicillin structures.²⁶ One group proposed that not only the R1 but also the R2 contributes to the epitope, and that this should be taken into account when assessing cross-reactivity.^{15,24} However, after the nucleophilic attack of the betalactam by the ϵ amino group of the carrier, the final structure is part of the betalactam and the R1 side chain.¹⁶ Thus, in this situation, it is not possible for the side chain at the R2 position to contribute to the epitope. In our study, we found that of those patients (N = 9) who were RAST-positive to more than 1 cephalosporin, 6 were RAST-positive to cephalosporins with the same R1 side chain, and 2 others were positive to cephalosporins with a similar R1 side chain; the cephalosporins in the remaining patient had different R1 and R2 side chains.

Regarding the RAST inhibition assays, we found that the behavior of cefaclor was unique because in 3 cases, cefaclor was the only relevant inhibitor, and in 1 case, more than 50% inhibition was obtained with 2 different cephalosporins, cefotaxime (case 1) and ceftazidime (case 3), which have different side chains. However, ampicillin, which has the same R1 side chain as cefaclor, had no relevant contribution. This is explained by the fact that in the determinant generated by cefaclor, the R1 side chain plus the remaining cephalosporin structure form part of the antigenic determinant, but for ampicillin, in addition to the side chain, the betalactam structure and the thiazolidine ring are both present.

Cefuroxime, a second-generation cephalosporin, was the most frequent culprit drug. In most instances, IgE antibodies also recognized cefotaxime, indicating a very high degree of cross-reactivity between their R1 side chains. In cefotaxime-positive cases, a very high cross-reactivity was observed with ceftriaxone, followed by cefuroxime. This indicates that RAST inhibition assays are in agreement with the fact that the C-7 substitution (at the R1 position) plays a dominant role in determining the specificity of immunologic reactions between individual cephalosporins and between penicillins and cephalosporins, to a greater degree than that observed for penicillins.²⁷ With this work, we have confirmed previous studies by our group, performed with synthetic cephalosporin derivatives, showing that recognition was mainly directed to the R1 side chain.¹⁶

In summary, in patients with a primary response to cephalosporins, selective recognition within the cephalosporin group exists, with good tolerance to penicillin determinants. Furthermore, within the cephalosporin group, selective recognition of the R1 side chain was observed in $\frac{2}{3}$ of the cases, with some degree of cross-reactivity between different cephalosporins, which almost always concerned cephalosporins with identical or similar R1 side chains. Accordingly, our recommendations are that in most patients with confirmed immediate hypersensitivity to cephalosporins, if skin tests to penicillin determinants are negative, penicillin can be administered safely. For

administration of other cephalosporins, the recommendation is to select a cephalosporin with a different R1 side chain.

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