

Detection of specific IgE to quinolones

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Background: In the last years, immediate reactions to quinolone antibiotics have been observed with increasing frequency, mainly urticaria, angioedema, and shock. No test was available because of the high incidence of false-positive results on skin tests. Thus the pathogenesis, value of diagnostic procedures, and cross-reactivity have not been evaluated in a systematic way.

Objective: We sought to assess whether these reactions are IgE mediated and whether an in vitro test for quinolone-specific IgE is useful in the diagnosis and understanding of cross-reactivity.

Methods: We assayed specific serum IgE to quinolones using epoxy-activated sepharose 6B as the solid phase in 55 patients with immediate adverse reactions; specificity of IgE binding was demonstrated by inhibition tests.

Results: The test yielded positive results in 30 (54.5%) patients who were tested 1 to 48 months after the reaction had occurred. The quinolone-specific IgE seems to disappear more slowly in atopic patients. The cross-reactivity between various quinolones allowed us to identify a common structural motif within quinolones that might be responsible for clinical and serologic cross-reactivity.

Conclusion: A substantial portion of immediate reactions to quinolones appear to be IgE mediated. Cross-reactivity of IgE among different quinolones is frequent and suggests that a common avoidance of quinolones should be attempted in all patients with respective symptoms. (*J Allergy Clin Immunol* 2004;113:155-60.)

Key words: Adverse drug reaction, serum IgE, quinolones

Quinolones form a family of synthetic antibiotics that has been in use since the early 1960s. For a long time, these antibiotics were only used for urinary tract infections. However, after the discovery of norfloxacin and subsequently of other fluoroquinolones, their use was increasingly extended because of their effectiveness against gram-positive and gram-negative bacteria that cause various systemic infections.

There are numerous reports of unpredictable adverse reactions to quinolones: often an immunologic mechanism has been suspected or demonstrated.¹ A high frequency of adverse reactions has been found in HIV-infected patients treated with ciprofloxacin.²⁻⁵ The most

frequently described reactions are immediate, suggesting a type I (IgE-mediated) allergic mechanism. Clinical manifestations include pruritus, urticaria, angioedema, and shock.⁶⁻¹⁹

Although certain authors have found skin tests (prick and intradermal) useful for the diagnosis of quinolone allergy,^{6,16} others have found that such tests often produce negative results.^{19,20} Skin tests have also been shown to have positive results in healthy control subjects.^{8,9,21} These false-positive results were probably triggered by a direct histamine release by quinolones.²² Attempts to detect specific IgE in vitro were without success.^{9,10} Thus challenge testing seems to be the only type of testing to prove an IgE-mediated sensitization.^{6,8,9,11,18}

In addition to immediate reactions, quinolones are also reported to elicit delayed immune reactions leading to a variety of symptoms, such as hepatitis, different forms of exanthema, nephritis, serum sickness, and blood cell dyscrasia.¹ In these reactions an immunologic mechanism has rarely been demonstrated, with the exception of positive photopatch test results in patients treated with lomefloxacin.²³

The majority of reports concern ciprofloxacin, which is the most commonly used quinolone. Other quinolones have also been reported to cause adverse reactions. For example, the fluoroquinolone temafloxacin was withdrawn from the world market because of the high frequency of severe and even fatal adverse reactions, at least some of which appeared to be immune mediated.^{24,25} Moreover, in 1999, trovafloxacin was removed from the European market, and its use was restricted in the United States because of severe, sometimes fatal, acute hepatitis.²⁶

In this study we report the detection of quinolone-specific serum IgE. Our data show that a high proportion of patients with immediate quinolone hypersensitivity have circulating quinolone-specific IgE antibodies and that these IgE molecules show a broad pattern of cross-reactivity with other quinolones.

METHODS

Patients

Of 5000 patients with adverse drug reactions analyzed, 55 reported 69 immediate adverse reactions to antibiotics of the quinolone family, mainly urticaria-angioedema (85%), sometimes with glottis edema (35%) or shock (13%). Sex distribution was as follows: 44 women and 11 men. The mean age was 44 years (range, 18-72 years). Twenty-three (42%) patients were considered atopic on the basis of positive skin test responses to inhalants allergens. Nine (16%) patients had experienced an adverse reaction to more than one quinolone, and 24 (44%) reported adverse reactions to

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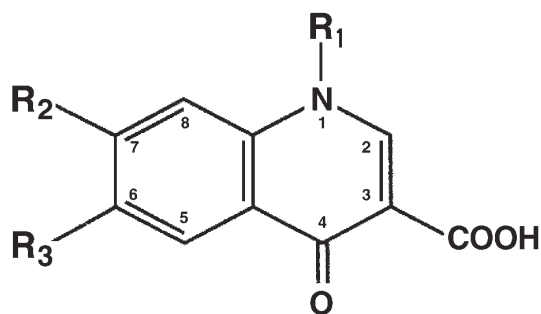


FIG 1. General structure of quinolones.

other nonquinolone drugs. Quinolones were prescribed mainly because of urinary (71%) or respiratory (21%) tract infections. In 64 (93%) of 69 reactions, the patients had not taken other drugs together with the quinolone. In 35 (51%) episodes symptoms appeared within 60 minutes after the intake of the drug. The quinolones suspected of causing the adverse reactions were ciprofloxacin ($n = 16$), cinoxacin ($n = 16$), lomefloxacin ($n = 9$), ofloxacin ($n = 7$), pipemidic acid ($n = 6$), pefloxacin ($n = 6$), norfloxacin ($n = 4$), nalidixic acid ($n = 2$), rifloxacin ($n = 2$), and enoxacin ($n = 1$). Two control groups were evaluated. The first group consisted of 22 atopic individuals with no history of adverse reactions to drugs, and the second group consisted of 10 individuals treated with quinolones without any adverse reaction.

This study was approved by the local ethical committee.

Reagents

The principle structure of quinolone is shown in Fig 1. The antibacterials evaluated are shown in Fig 2. They are characterized by different side chains in positions 1, 6, and 7 of the basic structure.

Pipemidic acid, norfloxacin, and nalidixic acid were purchased from Sigma-Aldrich S.r.l. (Milan, Italy), cinoxacin was from FIRMA S.p.a. (Florence, Italy), and ciprofloxacin was from Bayer-Miles-Pentex (Kankakee, Ill). Rifloxacin was donated by Mediolanum Farmaceutici S.p.a. (Milan, Italy), pefloxacin by Rhone-Poulenc Rorer (Milan, Italy), lomefloxacin by Searle Farmaceutici (Milan, Italy), and ofloxacin by Sigma-Tau Industrie Farmaceutiche Riunite S.p.a. (Pomezia, Italy). Sepharose EA 6B and human anti-IgE serum marked with iodine 125 were purchased from Pharmacia (Uppsala, Sweden).

Detection of specific serum IgE

Drug-specific serum IgE was determined by using an RIA. The solid phase was obtained by coupling the drug to sepharose epoxy-activated 6B through a spacer arm, according to the method of Baldo and Harle.²⁷ Rabbit-mouse anti-human IgE antiserum labeled with iodine 125 (Pharmacia) was used as the detecting antibody. Results are expressed as the percentage of the radioactivity bound to the solid phase in relationship to the total radioactivity introduced. Values of at least 3 times the level of normal serum (a pool of 2 sera of healthy, nonatopic individuals) were considered positive.²⁸ In addition, the patient's serum was also tested against a solid phase without drug and consistently resulted in values less than those with normal serum (data not shown).

IgE-binding inhibition test

The method described by Harle et al²⁹ was used. Briefly, the serum (50 μ L) was diluted as prescribed, incubated for 1 hour with 50 μ L of the drug, and then added to the solid phase. The test was subsequently carried out as for IgE determination.

Statistical analysis

The results are expressed as median values. Because the data were not distributed along the Gaussian curve, χ^2 analysis was used to assess the differences between groups. P values of less than .05 were considered significant (2-tailed χ^2 test).

RESULTS

Serum IgE to quinolones was detected for at least one quinolone in 30 (54.5%) of 55 cases (Table I).

The specificity of the assay was demonstrated by using inhibition tests. The serum of patient 20 was absorbed not only with the suspected drug, namely ciprofloxacin, but also with 5 structurally unrelated drugs (Fig 3). Serum was then assayed with the ciprofloxacin-sepharose solid phase. The maximum inhibition at a drug concentration of 1000 nmol was 85% with ciprofloxacin, 22% with rifampicin, 6% with cefuroxim, 4% with penicillin G, 3% with amoxicillin, and 2% with 4-aminoantipyrine.

In both control groups, the results of the search for serum-specific IgE to quinolones were negative, indicating that neither atopic status nor quinolone intake alone induces quinolone-specific IgE production.

Cinoxacin hypersensitivity

The first patients observed had severe symptoms after cinoxacin, but the *in vitro* test results with this drug were repeatedly negative in all patients. We therefore tested for the presence of IgE for other quinolones in these patients given the considerable structural analogy between the various molecules. We obtained positive results in 9 patients (nos. 7-15) with an uptake from 4.2% to 44.7% by using pipemidic acid and rifloxacin in the solid phase. To demonstrate the specificity of these results, we incubated the serum with cinoxacin and then assayed with sepharose-pipemidic acid and sepharose-rifloxacin solid phases. The results in the 2 patients considered (nos. 8 and 10) revealed high maximum inhibition values, ranging from 82% to 99% (Fig 4).

The explanation for this peculiar behavior perhaps lies in the chemical structure of cinoxacin (Figs 1 and 2): cinoxacin is the only quinolone lacking a side chain in position 7 of the quinolinic nucleus that is capable of binding to sepharose. Consequently, the cinoxacin molecule can only bind to the solid phase by means of the carboxyl group in position 3. Similarly, the assay with nalidixic acid yielded rather low counts, and results were positive only in certain patients, probably because the R2 side chain is a methyl group that does not allow for optimal binding to the solid phase. As a result, the epitope recognized by IgE seems to include the carboxyl group in position 3. An alternative explanation could be that cinoxacin is not able to bind to sepharose at all.

DISCUSSION

Our study demonstrates that immediate hypersensitivity reactions to quinolones may be due to an IgE-mediated immune mechanism. Quinolone-specific IgE was

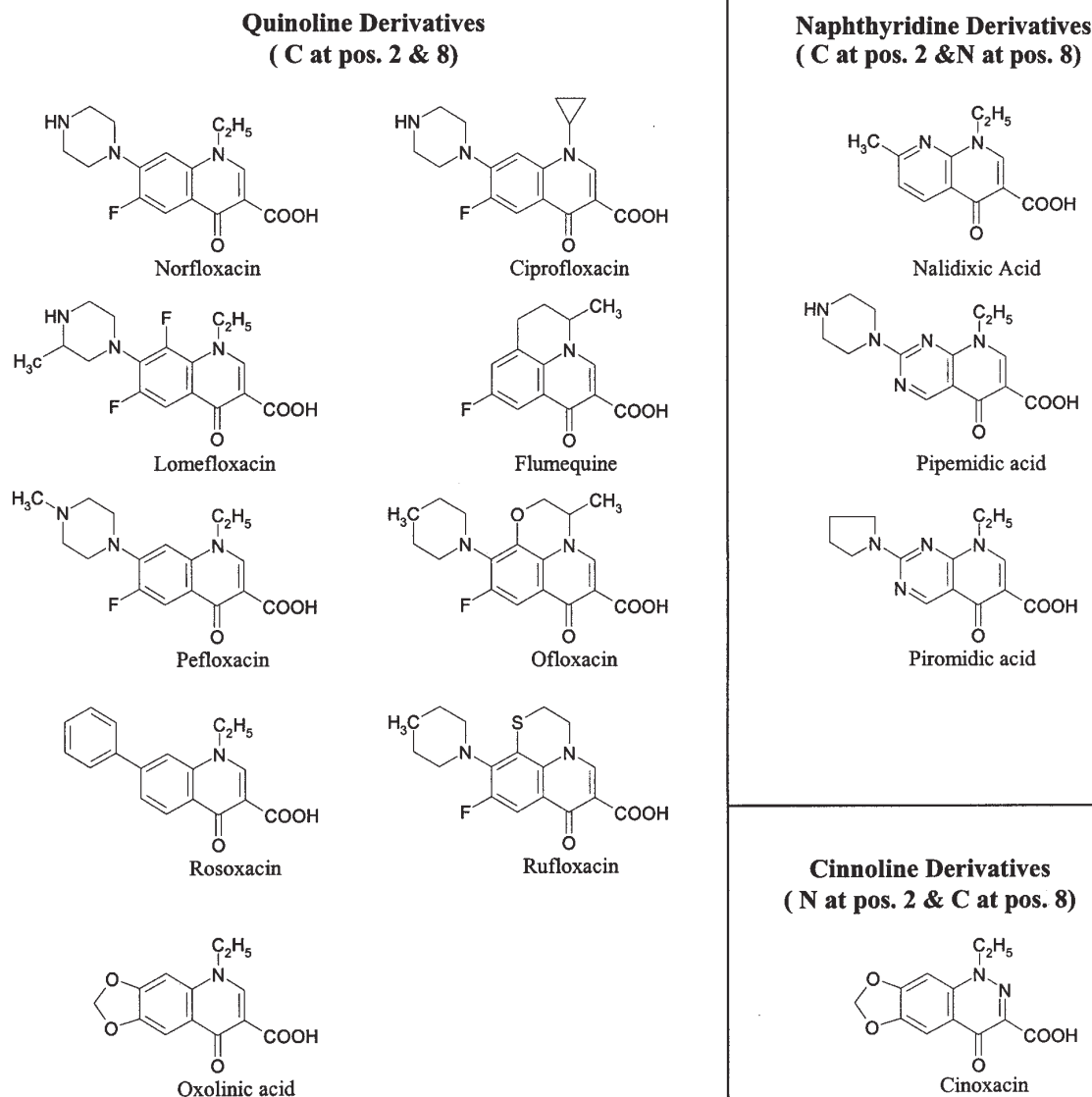


FIG 2. Structures of quinolones and fluoroquinolones.

detectable with an in vitro test, and broad cross-reactivity of these IgE with different quinolones was shown to exist. To our knowledge, these are the first data to unequivocally demonstrate an IgE-dependent mechanism against this group of drugs, which gain in importance because of their excellent antibacterial properties.

Our patients had, with very high likelihood, allergic reactions to quinolones: 62% had a documented previous exposure to quinolones. Patients had a typical clinical history of an immediate allergic reaction with a rapid onset after drug intake, and most patients took only the quinolone. Because the probability of a quinolone allergy was very high and because the majority had severe reactions (with glottis edema in more than one third of patients and shock or asthma in 17%), we were unable to perform provocation tests. Provocation tests with quinolones might be dangerous because even fatal adverse reactions have been reported.^{3,24,30-32}

Specific IgE was identified in 30 (54.5%) of 55 patients (IgE-positive group). We did not detect quinolone-specific IgE in 25 patients (IgE-negative group). There are several possible explanations for this. First, the reaction might actually be due to a pseudoallergic mechanism because quinolones are known to elicit false-positive results on intradermal skin tests.^{8,9,21} These drugs have a nonspecific capacity to release histamine from mast cells and basophils because the administration of very high oral doses in the dog (40-100 times the therapeutic dose) led to an increase in plasma histamine and generalized rash.²² Indeed, a previous quinolone exposure, which might have sensitized the patient, was higher in the IgE-positive than in the IgE-negative group (80% in the IgE-positive group and 44% in the IgE-negative group; $\chi^2 = 7.94$, $P < .01$). Second, some patients might react to low levels of drug-specific IgE that cannot be identified by means of in vitro tests detecting only free serum IgE but not cell-bound

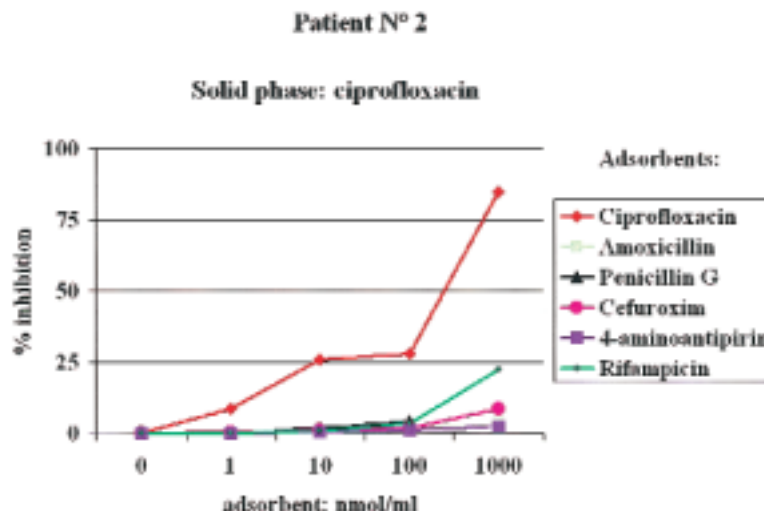


FIG 3. Inhibition of binding of IgE to the solid phase with ciprofloxacin by means of absorption with ciprofloxacin, amoxicillin, penicillin G, cefuroxime, 4-aminocapirine, and rifampicin.

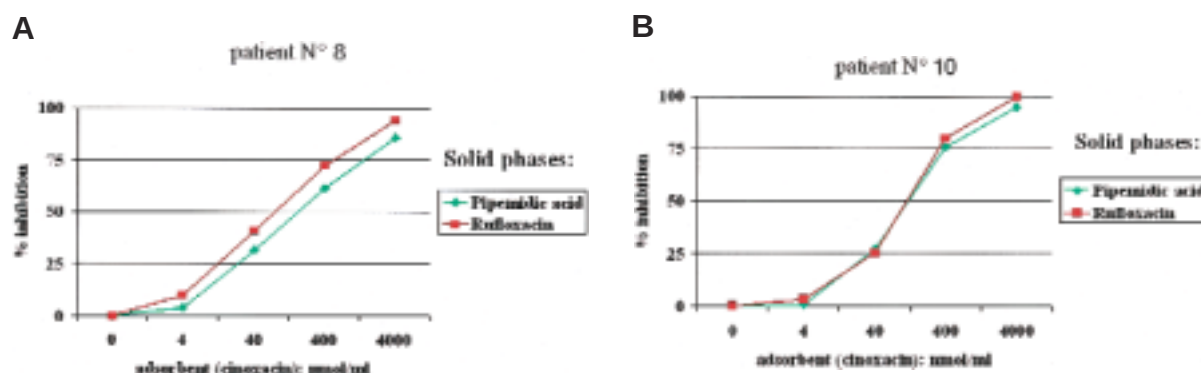


FIG 4. A, Inhibition of binding of IgE to the solid phase with pipemidic acid and rifloxacin by means of absorption with cinoxacin in patient 8. B, Inhibition of binding of IgE to the solid phase with pipemidic acid and rifloxacin by means of absorption with cinoxacin in patient 10.

IgE. These might nonetheless be patients with severe adverse reactions: in fact, the level of the specific serum IgE does not correlate with the severity of the adverse reaction. Considering only the patients tested within 8 months of the adverse reaction, the average percentage of bound radioactivity (level of specific IgE) in 7 patients with severe reactions (shock or asthma) was $14.1\% \pm 10\%$, whereas in 15 patients with less severe cutaneous reactions, it was $14.5\% \pm 10\%$.

Similar to the determination of other drug-specific IgE antibodies, the time interval between the adverse reaction and the blood sampling might be important because the serum-specific IgE level diminishes in the absence of contact with the allergen. In fact, we found a statistically significant difference between the average percentage of bound radioactivity (level of specific IgE) in the 22 patients who were sampled within 8 months of the adverse reaction ($14.4\% \pm 10\%$) versus the 8 patients who were sampled more than 8 months later ($8.1\% \pm 3\%$, $P = .095$). Indeed, the time lapse between the adverse reaction

and the blood sampling was shorter in the IgE-positive group (9.7 ± 14.4 months in the IgE-positive group and 15.6 ± 19.6 months in the IgE-negative group on average).

A further analysis of the IgE-positive group and the IgE-negative group revealed quite interesting parameters that distinguish them. As to the severity of the reaction, shock or asthma occurred more frequently in the IgE-positive group (9/35 [26%] episodes) but occurred in only 3 (9%) of 34 episodes in the IgE-negative group. Similarly, the number of patients hospitalized as a result of the adverse reaction was higher in the IgE-positive group (37%) than in the IgE-negative group (18%). The presence of atopy also differed: 50% of the IgE-positive group and 32% of the IgE-negative group were atopic. Atopy seems to prolong the persistence of drug-specific IgE: of the 18 patients examined more than 8 months after the adverse reaction, 8 showed specific IgE, and all were atopic. In 10 patients the assay result was negative, and only 3 of these were atopic. The probability of having a positive test result

TABLE I. Results of the assays for serum-specific IgE to quinolones in the IgE-positive group

Patient no.	Atopy	Total IgE (kU/L)†	Months‡	Drug taken	Drug-specific IgE to: (% bound/total radioactivity)*																	
					PIP	NS	RUF	NS	PEF	NS	NAL	NS	CIN	NS	LOM	NS	CIP	NS	NOR/OFL	NS		
1	Y	222	19	PIP	4.46	1.39	4.66	1.24	1.16	0.77	0.83	0.79										
2	N	29	1	PIP	14.27	1.11	7.88	1.52	5.41	0.74			0.29	0.29								
3	Y	804	12	RUF	10.60	1.01	7.50	1.80	2.10	0.35	0.38	0.21	1.24	0.42								
4	Y	363	48	PEF	13.80	1.40	10.80	1.60	4.95	0.86	0.32	0.32	0.64	0.54								
5	Y	109	48	PEF	6.00	1.40	6.42	1.62	3.40	0.87	0.29	0.32	0.44	0.54								
6	Y	704	2	PEF	16.38	1.37	8.30	1.30	2.70	0.50	0.65	0.37	0.55	0.21								
7	N	902	4	CIN	44.78	1.37	42.72	1.56	36.42	0.48	6.72	0.37	0.84	0.24								
8	N	258	3	CIN	25.50	1.40	19.20	1.60	9.00	0.71	1.44	0.33	0.40	0.28								
9	Y	445	2	CIN	23.60	1.47	8.38	1.80	2.77	0.75	0.40	0.17	0.50	0.13								
10	N	40	5	CIN	15.90	0.98	17.34	1.35	4.40	0.54	0.49	0.37	0.21	0.21								
11	N	38	1	CIN	5.48	1.22	5.11	1.68	1.85	0.67	0.36	0.44	1.05	0.50								
12	N	74	4	CIN	4.42	1.37	10.80	1.30	0.95	0.48	0.30	0.37	0.38	0.39								
13	N	76	1	CIN	4.58	1.37	4.20	1.56	1.19	0.48	0.34	0.37	0.39	0.21								
14	N	23	8	CIN	11.27	1.28	3.90	1.70	0.81	0.76	0.46	0.41	0.23	0.10								
15	N	92	5	CIN	6.24	1.27	4.07	1.73	1.14	0.49	0.33	0.27										
16	Y	991	1	LOM	17.04	1.22	15.17	2.17	6.61	1.06	2.14	0.68			23.11	2.57						
17	Y	293	36	LOM	5.37	1.63	4.53	1.62	1.17	1.01					6.46	2.09						
18	Y	285	24	LOM	6.94	1.52	7.47	1.96	1.72	0.87	0.62	0.49	0.95	0.44	6.70	2.20						
19	N	77	1	LOM	4.22	1.42	5.02	2.21							7.60	2.50						
20	N	136	1	CIP	24.15	1.18	12.38	1.31	20.04	0.77	0.90	0.79					24.86	1.15				
21	Y	178	12	CIP	5.18	1.27	3.14	1.68	1.00	0.67	0.36	0.44					1.53	0.89	4.69	2.10		
22	Y	196	39	CIP	4.28	1.29	4.59	1.04									9.94	3.16				
23	N	187	2	CIP	1.99	1.44	4.21	1.06	1.27	0.86							1.58	1.20				
24	Y	229	2	CIP	3.76	1.16	5.64	1.06									1.77	1.13				
25	N	355	1	CIP	10.48	1.62	7.21	2.00	3.14	0.92							2.80	0.75				
26	N	38	3	CIP	13.20	1.30	9.25	1.41									10.40	0.82				
27	Y	330	1	CIP	3.36	1.44	2.73	1.23	1.45	0.84							3.41	1.09				
28	N	276	2	NOR	7.56	1.54	7.00	1.87	1.98	0.88	0.46	0.46	0.49	0.50					7.54	1.51		
29	Y	122	1	NOR	18.30	1.41	12.20	1.67											24.40	0.83		
30	Y	461	1	OFL	11.22	1.87	8.85	2.28	1.18	0.59	0.16	0.17	0.17	0.16					1.92	0.32		

PIP, Pipemidic acid; NS, normal serum, pool of nonatopic subjects without adverse reactions to drugs; RUF, rifloxacin; PEF, pefloxacin; NAL, nalidixic acid; CIN, cinoxacin; LOM, lomefloxacin; CIP, ciprofloxacin; NOR, norfloxacin; OFL, ofloxacin.

*Drug coupled to the solid phase. Values are positive when equal to or greater than triple the value of normal serum. The sera of the 2 control groups (ie, individuals exposed without reaction and atopic patients without history of reactions) resulted in values lower than those of normal serum.

†Normal value: less than 100 kU/L.

‡Months elapsed between adverse reaction and bleeding for assay.

after 8 months was therefore 73% (8/11) in the atopic patients and zero (0/7) in the nonatopic patients ($\chi^2 = 8.35$, $P < .001$). On the other hand, if the test is performed within 8 months of the adverse reaction, the chances of obtaining a positive result are the same in the 2 groups (7 positive results among 12 atopic patients = 58% vs 15 positive results among 25 nonatopic patients = 60%).

Our data also suggest that the different quinolones might have a distinct sensitizing potential: cinoxacin was significantly more represented as the causative quinolone in the IgE-positive group than in the IgE-negative group (12 vs 4 patients, $P < .01$). Moreover, cinoxacin and pefloxacin are associated with a more rapid onset of symptoms of an adverse reaction after drug intake and a higher level of drug-specific IgE.

Cross-reactivity is a common problem in drug hypersensitivity, and the common core structure of quinolones predisposes them for cross-reactivity. Indeed, various authors have claimed cross-reactivity between

quinolones on the basis of clinical data.^{6,9,33-38} Our data support this notion because several patients reported a reaction with more than one quinolone (9/55 [16%]). Moreover, the majority of our patients revealed IgE toward more than one quinolone (24/30 [80%]). Cross-reactivity between quinolones was also demonstrated in 2 patient sera (nos. 8 and 10) by using the inhibition assay with cinoxacin, which inhibited the IgE binding toward both pipemidic acid and rifloxacin (Fig 4).

In conclusion, quinolones belong to those groups of drugs that might elicit an IgE response and anaphylaxis-like symptoms. These can be detected by using an in vitro assay, which is particularly useful because skin tests are not reliable. A further development of this test (ELISA instead of RIA) might make it more widely acceptable and a helpful tool in the diagnosis of quinolone hypersensitivity. Cross-reactivity within the quinolone group is common, suggesting that a strict avoidance of all quinolones is advisable in patients with quinolone-induced allergies.

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