

In Vivo Diagnostic Tests in Adverse Reactions to Quinolones

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■ Abstract

Background and objective: Contradictory reports of the sensitivity of skin tests in quinolone allergy have been reported. Our objectives were to describe the outcome of quinolone skin and challenge tests in patients consulting because of a history of adverse reaction to quinolone and to compare the outcome of quinolone skin tests and challenge tests in the subsample of patients who had undergone both tests.

Methods: We reviewed skin and challenge test results of all patients who consulted at our allergy service over the last 5 years because of a history of quinolone adverse reaction in the form of urticaria or anaphylaxis within 1 hour of drug intake (group 1), urticaria or maculopapular eruption between 1 and 24 hours after intake (group 2) or after 24 hours had passed (group 3), or atypical symptoms (group 4).

Results: A total of 71 cases were identified: 27, 8, 24 and 12 in groups 1 through 4, respectively. Skin tests were performed in all patients, with positive results in 31 patients. In group 1, 62.9% of these patients showed positive skin tests and 22.2% showed positive challenge tests, whereas in the other 3 groups, about 30% of patients had positive skin tests and a variable percentage (from 0% to 4.1% depending on the group) had positive challenge tests. Quinolone challenge tests were performed in 10 patients with positive skin tests (5 of them with positive results) and in 34 patients with negative skin tests (2 of them with positive results).

Conclusions: A highly suggestive history of quinolone allergy is more frequently associated with positive skin tests and positive challenge tests. Therefore, skin tests help to predict the result of the challenge test.

Key words: Adverse reaction. Challenge test. Quinolones. Skin test.

■ Resumen

Antecedentes y objetivo: Se han publicado estudios contradictorios sobre la sensibilidad de las pruebas cutáneas en la alergia a quinolonas. Nuestros objetivos son describir los resultados de las pruebas cutáneas y de exposición en pacientes con una reacción adversa a quinolonas y comparar los resultados de las pruebas cutáneas y de las pruebas de exposición en la muestra de pacientes en los cuales se llevaron a cabo ambas pruebas.

Métodos: Revisamos los resultados de las pruebas cutáneas y de exposición de los pacientes que consultan en nuestro Servicio durante los últimos cinco años por una reacción adversa a quinolonas: urticaria o anafilaxia en la primera hora tras la toma del fármaco (grupo 1), urticaria o erupción maculopapulosa entre la primera y 24 horas (grupo 2) o pasadas las primeras 24 horas (grupo 3) y síntomas atípicos (grupo 4).

Resultados: Se detectaron un total de 71 casos (27, 8, 24 y 12 del grupo 1 al 4 respectivamente). Se realizaron pruebas cutáneas a todos los pacientes resultando positivas en 31. Si nos fijamos en el grupo 1, el 62.9% de estos pacientes mostraron pruebas cutáneas positivas y el 22.2% pruebas de exposición positivas. Estos porcentajes contrastan los de los otros tres grupos, los cuales mostraron en torno al 30% de pruebas cutáneas positivas y porcentajes variables (del 0 al 4.1% dependiendo del grupo) de pruebas de exposición positivas. Se realizaron pruebas de exposición en 10 pacientes con pruebas cutáneas positivas (5 con resultado positivo) y en 34 pacientes con pruebas cutáneas negativas (2 con resultado positivo).

Conclusiones: Una historia clínica altamente sugestiva de alergia a quinolonas se asocia más frecuentemente a pruebas cutáneas y de exposición positivas. Por lo tanto las pruebas cutáneas ayudan a predecir el resultado de la prueba de exposición.

Palabras clave: Reacción adversa. Prueba de exposición. Quinolonas. Pruebas cutáneas.

Introduction

Quinolones are antimicrobial agents with a broad range of activity against both gram-negative and gram-positive bacteria [1]. They are fairly safe, with an incidence of adverse drug reactions between 2% and 10% [2,3]. These adverse reactions include gastrointestinal complaints (nausea, abdominal pain, diarrhea), central nervous system symptoms (sleep disorders, headaches, reversible psychotic reactions such as hallucinations and agitation, convulsions), skin symptoms (eg, maculopapular or urticarial skin rashes [2], vasculitis [4,5], phototoxic or photoallergic dermatitis [6,7] and anaphylactoid reactions [8]). Immediate hypersensitivity-type reactions such as skin rashes, pruritus, severe respiratory distress and shock have been reported in less than 2% of patients receiving these drugs [9].

Quinolone allergies have been diagnosed by various methods: prick tests, patch tests, determination of specific immunoglobulin (Ig) E, and the histamine release test [10]. Contradictory results regarding the sensitivity of skin testing in quinolone allergy have been reported [11-14], and skin tests have led to positive results in healthy control subjects [10,15-16]. For these reasons, challenge testing seems to be the only way to detect an IgE-mediated sensitization to these drugs [10,12,13,15].

However, since a challenge test entails a certain amount of risk, we were interested in clarifying the usefulness of skin tests in diagnosing quinolone allergy. The objectives of this study were first to describe the outcomes of quinolone skin tests and quinolone challenge tests in a series patients consulting because of a history of adverse reaction to a quinolone and, second, to compare the outcome of quinolone skin tests and challenge tests in the subsample of patients who had undergone both tests.

Methods

This was a retrospective analysis of clinic cases. We collected records of all patients who had attended our allergy clinic in the last 5 years for a history of any adverse reaction to

quinolones: anaphylaxis, bronchospasm, rhinoconjunctivitis, laryngeal edema, urticaria, maculopapular eruption, isolated generalized pruritus, gastrointestinal pain, nausea, vomiting, and diarrhea. Cases in which both a drug challenge test and skin tests had been carried out and in which reactions occurred within 24 hours after the last administration of the drug were identified. Thus, patients whose reactions occurred more than 24 hours after the last drug administration and patients whose symptoms disappeared without cessation of the suspected drug, were excluded. The following patients were also excluded: those who had experienced several life-threatening skin reactions (including vasculitis, exfoliative dermatitis, toxic epidermal necrolysis or Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis), as these were contraindications to challenge testing, and those declining the drug allergy study.

The patients were classified into 4 groups as follows: a) group 1 patients had immediate adverse reactions, specifically urticaria or anaphylaxis occurring within 1 hour of taking the first dose of a drug, b) group 2 patients had accelerated reactions involving urticaria or maculopapular eruptions that occurred within 1 and 24 hours of the first dose, c) group 3 patients had urticaria or maculopapular eruptions that occurred between 24 hours of taking the first dose and 24 hours after the last administered dose, and d) group 4 patients had atypical symptoms, such as isolated gastrointestinal pains and isolated generalized pruritus.

Skin tests with the quinolone involved and, in most of the patients, with at least 3 other quinolones were carried out on the volar side of the forearm according to published procedures [17]. All the quinolones were initially tested by prick testing, and reactions were considered positive when a wheal greater than 3 mm in diameter was present 20 minutes later. When prick test responses were negative, and if the drug was available in an injectable solution, 0.05 mL of the drug solution was injected intradermally. Once again, wheals were read 20 minutes after the injection and considered positive when greater than 5 mm. Histamine (10 mg/mL) was used for the positive control in the prick test and normal saline was used for the negative control in the prick and intradermal tests. Twelve subjects with no previous history of quinolone allergy

Table 1. Quinolone Skin Test Concentrations

Drug	Concentrations	
	Prick	Intradermal
Ciprofloxacin	0.02 mg/mL	0.02 mg/mL
Norfloxacin	Tablet, 400 mg suspended in saline solution	NP
Ofloxacin	Tablet, 400 mg suspended in saline solution	NP
Moxifloxacin	Tablet, 400 mg suspended in saline solution	NP
Levofloxacin	5 mg/mL	0.05 mg/mL
Pipemidic acid	Tablet, 400 mg suspended in saline solution	NP
Trovafloxacin	Tablet, 200 mg suspended in saline solution	NP

*NP indicates not performed. (Intradermal tests were not performed when the drug was unavailable as an injectable solution.)

served as a control group. Drug concentrations used in prick and intradermal tests are summarized in Table 1.

Regardless of skin test results, oral or parenteral challenges with the quinolone involved were performed in some patients. The drug challenge tests consisted of ingesting or injecting increasing doses of the suspected culprit drug once every 30 minutes until the usual daily dose had been administered or symptoms of a drug reaction occurred. The drug challenge test result was considered positive if any of the symptoms or signs of an immediate drug reaction described previously were documented up to 24 hours after the last dose was administered. The test was considered negative if no sign of drug hypersensitivity occurred after the usual daily dose had been administered.

The patients' written informed consent to skin and challenge testing was obtained. Complete resuscitation equipment was prepared.

All the skin and challenge test results were reviewed by the authors of this report. Descriptive statistics for patient and clinical characteristics and skin and challenge test results are expressed as percentages and medians.

Results

A total of 71 patients (46 women and 25 men) were included. Ages ranged from 24 to 90 years (median, 59 years; interquartile range, 44.75-69.25 years). The drugs implicated were ciprofloxacin in 26 cases (36.6%), moxifloxacin in 17 (23.9%), norfloxacin in 14 (19.7%), ofloxacin in 8 (11.2%), levofloxacin in 2 (2.8%), pipemidic acid in 3 (4.2%), and trovafloxacin in 1 (1.4%). According to adverse reaction type, the patients were classified in 4 groups: 27 in group 1, 8 in group 2, 24 in group 3 and 12 in group 4 (Table 2).

Quinolone skin tests were performed in all patients and in 44 patients at least one challenge test was performed. The

skin and challenge test results according to reaction type are summarized in Table 2. In group 1, 62.9 % of these patients had positive skin tests and 22.2% had positive challenge tests. In the other 3 groups about 30% of the skin tests were positive and a variable percentage (from 0% to 4.1 % depending on the group) had positive challenge tests.

Most of the patients with positive skin tests showed positivity with more than one quinolone. The results and diagnoses for the 31 patients with positive prick or intradermal skin test results are shown in Table 3.

The skin tests performed in the 12 controls were negative with ciprofloxacin, levofloxacin, and norfloxacin in all the cases. Five controls, however, had positive prick tests with moxifloxacin, 3 with ofloxacin, and 1 with pipemidic acid.

A challenge test was only carried out in 10 of the 31 patients with positive skin tests: 5 had positive challenge test results and 5 had negative results. Challenge tests were performed in 34 out of 40 patients with negative skin tests: 2 with positive results and the remaining 32 patients with negative results. One of the 2 patients with positive challenge test results belonged to group 3 (micropapulous and pruriginous eruption 4 days after treatment with norfloxacin) and the other case belonged to group 1 (generalized nettle rash and face angioedema after the first ciprofloxacin dose). All the positive challenge tests occurred in the hour following the first or second dose and consisted of hives and pruritus; all responded well and rapidly to antihistamines.

In the 44 patients in whom a challenge test was performed, only 2 patients with negative skin tests (5%) had positive challenge tests whereas 5 (50%) of the patients with positive skin tests had positive challenge tests.

Finally, 34 patients were diagnosed with quinolone hypersensitivity: 21 of these 34 patients were only diagnosed by means of positive skin tests, 7 by means of challenge tests (5 with positive skin tests and 2 with negative skin tests), and

Table 2. Results of Challenge Tests According to the Type of Allergic Reaction or Timing and According to Skin Test Positivity or Negativity

Adverse Reaction Type	Skin Test Result	Challenge Test Result			Total
		Positive	Negative	Not Performed	
Immediate (group 1)	Positive	5	1	11	17
	Negative	1	4	5	10
	Total	6	5	16	27
Accelerated (group 2)	Positive		1	2	3
	Negative		5		5
	Total		6	2	8
After 24 hours (group 3)	Positive		1	6	7
	Negative	1	15	1	17
	Total	1	16	7	24
Atypical symptoms (group 4)	Positive		2	2	4
	Negative		8		8
	Total		10	2	12

Table 3. Characteristics of Skin Tests, Challenge Tests and Final Diagnosis in Patients with Positive Skin test Results*

Reaction Type	Culprit Drug	Patient No.	Skin Test				Challenge Test When Performed		Diagnosis of Allergy
			Prick Test		Intradermal		Positive	Negative	
			Positive	Negative	Positive	Negative			
Immediate (group 1)	Ciprofloxacin	1	O,L,I,M	N,C	C		-	-	yes
		2	O,L,M	N,C		C	M		yes
		3	C	N	-	-	-	-	yes
		4	O,M	N,C,L		C,L	C		yes
		5		N,C	C		-	-	yes
	Norfloxacin	6	O,L,N,G,M	M	-	-	-	-	yes
		7	O,L	N,C,M	-	-		N	no
	Ofloxacin	8	O,L,M	N,C	-	-	-	-	yes
		9	O	N,P,C	C		-	-	yes
	Moxifloxacin	10	O,L,M	M,C	C		-	-	yes
		11	O,L,M	N,C,G		C	-	-	yes
		12	L,M	N,C,O		C	-	-	yes
		13	O,M,C	N,L		L	M,L	C	yes
		14	O,M	N,C,L		C,L	M	L,C	yes
		15	M	N,C,L,O	C	L	M		yes
		16	O,M	N,C,L		C,L	-	-	yes
	Pipemidic acid	17	O,C,P	L,M		L	-	-	yes
Accelerated (group 2)	Ciprofloxacin	18	O,C,	N,P	-	-	-	-	yes
		19	N	C	C		-	-	yes
	Norfloxacin	20	L	N,C,L,M		C		C,N	no
After 24 hours (group 3)	Ciprofloxacin	21	O,M,	N,C,L	C	L	-	-	yes
		22		N,C	C		-	-	yes
	Norfloxacin	23	O,L,G	N,C		C	-	-	yes
		24	O,L,M	N,C		C		C,N	yes
	Ofloxacin	25		C,O	C				yes
	Moxifloxacin	26	L,M	N,C,O		C	-	-	yes
Pipemidic acid	27	O,M	N,L,C,P		C,L		P	no	
Atypical symptoms (group 4)	Norfloxacin	28	O,L,M	N,C		C		N	no
	Ofloxacin	29	O,L,M	N,C		C	-	-	yes
	Moxifloxacin	30	O,L	N,C, M	C		-	-	yes
		31	M	N,C,O,L		C,L		M	no

*O indicates ofloxacin; L, levofloxacin; M, moxifloxacin; N, norfloxacin; C, ciprofloxacin; G, grepafloxacin; P, pipemidic acid.

the remaining 6 patients by means of a suggestive clinical history despite having negative skin tests.

Thirty-seven patients were not quinolone hypersensitive: all of them had negative challenge tests and only 5 patients had positive skin tests.

Discussion

The descriptive statistics compiled for our series of 71 patients with reactions to a quinolone over a period of 5 years showed that these adverse reactions were more frequent in women (1.8:1) and in elderly patients. Ciprofloxacin and

moxifloxacin were the drugs most often implicated. Challenge tests were performed in less than half of the patients because the authors thought that risk was not justified in the others.

The association of immediate adverse reactions (group 1) with positive skin test results, suggested an IgE mediated mechanism. This finding contrasts with certain other reports that discarded the usefulness of skin tests for quinolone allergy diagnosis and affirmed that a challenge test is the only way to demonstrate quinolone allergy [10,18-21]. However, our finding is consistent with the results of other reports that demonstrate the value of skin tests to detect quinolone allergy [22]. Some patients with immediate adverse reactions had negative skin tests, however. They might have had pseudoallergic reactions (in which clinical

manifestations mimic IgE-mediated events but the initiating event does not involve an interaction between the drug and drug-specific IgE antibodies) or to an interaction between a metabolite of the drug (rather than the low molecular weight quinolone itself) and IgE; alternatively, it might be attributable to the lack of sensitivity of skin tests.

On the other hand, a third of patients belonging to the other 3 groups had positive skin test results. In some cases this would be consistent with IgE mediated accelerated reactions but in the main, it would be consistent with the lack of specificity of skin tests [10,19,21] or with insufficiency of information in the case history.

The main findings of the analysis of outcomes of both skin and challenge testing suggest that quinolone skin tests are a useful tool for the study of hypersensitivity to quinolones, helping in the decision of whether it is advisable or not to perform the challenge test. So, a negative skin test result predicted a negative challenge test result in 94% of the challenged sample and only 5% of patients with a negative skin test had a positive challenge test, whereas 50% of patients with a positive skin test had a positive challenge test. This report also shows that a negative drug provocation test result is important to a patient with a suspected drug allergy because a nonhypersensitive patient does not need to avoid this drug in the future; Mesaad et al [23] emphasized this after they used challenges to rule out quinolone allergy in 75% of their patients. We were able to rule out quinolone allergy in 37 of the 71 patients who consulted for a history of adverse reaction to a quinolone thanks to challenge tests.

The aim of diagnostic skin and challenge procedures is to distinguish adverse drug reactions such as intoxication and pharmacological intolerance from pseudoallergy or allergy [24]. Currently, oral challenge testing is considered by some authors to be the only reliable procedure for the diagnostic evaluation of allergic reactions to quinolones. The European Network for Drug Allergy of the European Academy of Allergology and Clinical Immunology recommends the use of drug challenge tests to confirm drug hypersensitivity reactions reported clinically [25], although this is controversial because in some cases such tests would be dangerous, in particular with regard to quinolones [11,26]. For example, we did not carry out challenge tests on 6 patients with negative skin tests and the challenge test was only carried out in 10 patients with positive skin tests, because the physician who attended and diagnosed those patients decided in each case if a challenge test should be performed given the patient's medical history. All the patients with negative skin tests and challenge tests not performed presented a history of severe anaphylaxis after the first drug dose and half of patients with positive skin tests and challenge test not performed belonged to group 1 (patients with a history highly suggestive of allergy). In our study, after choosing the candidates for challenge testing carefully, we only observed mild reactions. All the positive challenge tests occurred in the hospital, after the first or second challenge doses; reactions consisted of urticaria and responded well to antihistamines. We think that the percentage of patients with positive skin tests and a positive challenge test might have differed significantly if we increased the number of challenged patients but it would not have been clinically advisable.

The specificity of the skin test was low, as a positive result only predicted a positive challenge test in 50% of the patients

who underwent that procedure; moreover, we also found false positive skin test results in control patients. This seems to be due to nonspecific histamine release by quinolones because of direct mast cell activation. Since in basophilic leukocytes this direct histamine release does not seem to occur, a basophilic leukocyte histamine release test might be suitable to detect actual IgE-mediated sensitization to quinolones in certain patients with anaphylactoid reactions. With respect to the problem of specificity, we would like to emphasize that a wheal diameter of 4 mm in the prick test and 6 mm in the intradermal test was the usual size in false positive patients, whereas the wheal sizes were usually greater in true positives. We therefore think that it would be necessary to standardize the dilutions used in quinolone skin testing in order to increase the specificity of the tests and avoid false positives.

Although the aim of this study was not to investigate the existence of cross-reactivity among quinolones, we noted that the majority of the patients with positive skin tests had a positive test with more than 1 quinolone. Nevertheless, in patients 13 and 14, who had challenge tests performed with more than 1 quinolone, cross-reactivity was demonstrated in only 1 case, between moxifloxacin and levofloxacin. That cross reaction was ruled out in the other patient and a cross-reaction between moxifloxacin and ciprofloxacin was ruled out for both (Table 3). There are few reports of cross-reactivity between quinolones and they are contradictory [10,22,27]; some patients have shown a high degree of cross-reactivity between different groups of quinolones but others have been allergic to 1 quinolone but tolerant of others. Because the tolerance to other quinolones is unpredictable, it is advisable that the prohibition be made extensive to all quinolones in cases of adverse reactions to one of them.

A limitation of our study is that we did not perform *in vitro* tests. Other authors have reported contradictory results after such studies: Manfredi et al [28] published a study of specific IgE antibodies against quinolones in which a high proportion of patients (54.5%) with immediate hypersensitivity to quinolones also had quinolone-specific circulating antibodies, but other authors have been unsuccessful when they tried specific IgE determination, possibly due to the difficulty of the binding of quinolone to the solid phase [6,10].

In conclusion, a highly suggestive history of quinolone allergy is more frequently associated with positive skin and challenge test results. Our report suggests that skin tests seem to be a useful tool for the study of hypersensitivity to quinolones, helping in the decision of whether it is advisable to perform a challenge test. For this reason it is advisable to take a thorough clinical history and skin tests with several quinolones in order to guide the diagnostic study before an oral or parenteral challenge test is carried out.

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