

Hypersensitivity reactions to quinolones

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Purpose of review

The purpose of this review is to examine in detail the new advances in the pathomechanisms and diagnosis of immediate and nonimmediate hypersensitivity reactions to quinolones, as well as analyze cross-reactivity among different quinolones.

Recent findings

Hypersensitivity reactions to quinolones, especially anaphylactic reactions, have become more common in the past decade. This phenomenon could be related to their increased consumption. Although attempts have been made to standardize skin testing, the diagnosis of immediate hypersensitivity reactions to quinolones is mainly based on drug provocation. Some in-vitro, radioimmunoassay and basophil activation tests have also been used for diagnostic purposes, with results indicating that they could be complementary to in-vivo tests. Cross-reactivity seems to exist between first and second-generation quinolones, with lower levels with the third and fourth generations. However, no general rules exist for predicting cross-reactivity and it needs to be analyzed patient by patient. Nonimmediate hypersensitivity reactions also exist, especially maculopapular exanthema and fixed drug eruptions, and a T-cell mechanism has been demonstrated.

Summary

Over the past decade the number of hypersensitivity reactions to quinolones has increased. These reactions can be severe and diagnosis difficult to confirm. Although new in-vitro tests hold promise, drug provocation testing remains the most frequently used and reliable diagnostic method.

Keywords

cross-reactivity, hypersensitivity, IgE, quinolones, T cells

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Introduction

Quinolones have been used for over 30 years to treat a wide range of infections, with nalidixic acid being the first commercialized quinolone. The addition of fluoride to the original molecule produced the fluoroquinolones, which had an improved antimicrobial spectrum [1].

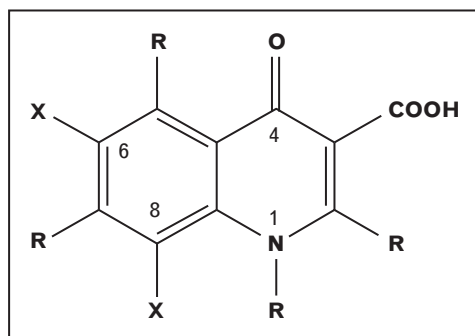
The basic structure of quinolones is formed by a bicyclic skeleton, one pyridone and another aromatic. The pyridone presents a nitrogen at position 1, a carboxyl group at position 3, and a carbonyl group at position 4 [2]. From a chemical point of view, the structural differences between the quinolones are derived from the number and position of nitrogen atoms, the side chains, and the fluoride atoms in the structure (Fig. 1).

Quinolones, such as ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin, are highly consumed, though others are less often used, or have even been withdrawn because of

toxicity, such as gatifloxacin, gemifloxacin, enoxacin, pefloxacin, temafloxacin, trovafloxacin, sparfloxacin, lomefloxacin, grepafloxacin, clinafloxacin. Indeed, fluoroquinolones, which have a second halogen substituent at position C-8, like lomefloxacin, are considered the most toxic. The classification of the most often used quinolones in different generations [3], according to their main antibacterial activity as well as their chemical structure, is shown in Table 1.

Their mechanism of action is the inhibition of DNA synthesis by inhibiting topoisomerase II (DNA-Gyrase) in gram-negative and topoisomerase IV in gram-positive bacteria, resulting in rapid bacterial death [4]. Fluoroquinolones are well absorbed after oral administration, with a bioavailability ranging from 50 to 100%, with low plasma protein binding and are excreted by the kidneys, by nonrenal pathways or both [2]. Quinolones are relatively well tolerated antibiotics, with most adverse effects being mild, involving the gastrointestinal or central nervous systems, allergy and phototoxicity [5].

Figure 1 General structure of quinolones



Epidemiology

The frequency of hypersensitivity reactions to quinolones seems to have increased in the past decade, and quinolones are now probably the nonbeta-lactam antibiotic most frequently involved in allergic reactions. In our population (Spain), quinolones are the third leading cause of confirmed hypersensitivity to drugs, after anti-inflammatory drugs and beta-lactams, having increased from 0.53% in 2005 to 5.96% in 2009 (data not published).

Most hypersensitivity reactions to quinolones are of the immediate type. On the basis of spontaneous reports of anaphylaxis induced by quinolones, since 2000 there has been an increase in the total number of cases of anaphylaxis, mainly from moxifloxacin [6]. In fact, moxifloxacin was involved in 54% of all cases, levofloxacin in 15%, ciprofloxacin in 13% and ofloxacin in 10% [6]. These results are supported by studies recently carried out in Spain in a large group of patients with immediate hypersensitivity reactions to quinolones, with moxifloxacin being involved in 63.2% of cases, followed by ciprofloxacin in 28.9% and levofloxacin in 7.9% [7^{••}]. Moreover, reactions induced by moxifloxacin were more severe, with 75% of reactions comprising anaphylaxis or anaphylactic shock, versus 54% in those induced by ciprofloxacin [7^{••}].

Nonimmediate reactions to quinolones are less frequent than immediate reactions. These nonimmediate reactions include maculopapular exanthemas [8,9], fixed drug eruptions [10–12], acute generalized exanthematic pustulosis (AGEP) [8,13] and Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [14–16].

Allergic reactions

Allergic reactions to quinolones can be classified as immediate (appearing within 1 h after drug intake), characterized by the presence of urticaria and anaphylaxis; or nonimmediate reactions (appearing more than 1 h after drug intake), with maculopapular exanthema and fixed drug eruptions being the most frequent clinical symptoms [17].

Key points

- IgE-mediated hypersensitivity reactions to quinolones seem to have increased over the past decade.
- The diagnosis can be difficult because skin testing can induce false-positive results.
- Some in-vitro methods such as radioimmunoassay and basophil activation tests may become helpful to improve diagnosis.
- The pattern of cross-reactivity is complex and difficult to predict.
- Nonimmediate reactions to quinolones are less frequent and in some cases T-cell mechanisms have been demonstrated.

laxis; or nonimmediate reactions (appearing more than 1 h after drug intake), with maculopapular exanthema and fixed drug eruptions being the most frequent clinical symptoms [17].

Immediate reactions

Immunological mechanisms, clinical symptoms and diagnosis of immediate reactions are discussed, especially focusing on recent findings regarding in-vitro diagnostic methods.

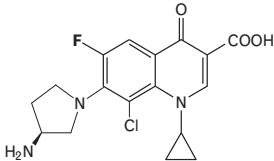
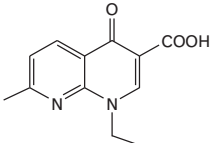
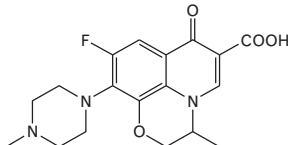
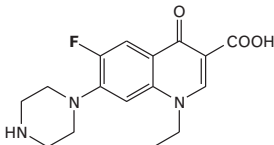
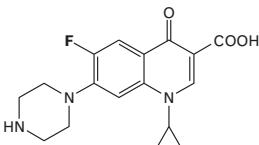
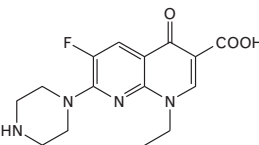
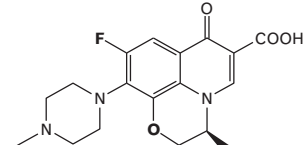
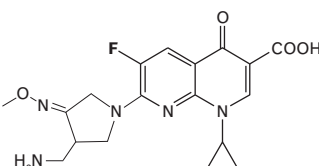
Mechanisms involved

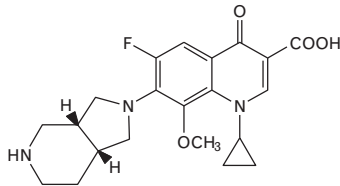
The mechanisms underlying immediate allergic reactions to quinolones are difficult to demonstrate and, although the clinical symptoms are indicative of an IgE-mediated reaction, it is nevertheless difficult to show the presence of specific IgE [7^{••},9]. In a study reported by Sachs *et al.* [6] 13% of cases of anaphylaxis attributed to quinolones occurred within the first 3 days of treatment, and had never received treatment with this particular quinolone, suggesting that an alternative mechanism to IgE recognition may be involved.

Previous attempts to demonstrate the presence of specific IgE to quinolones were without success [18,19]. The first evidence of the presence of specific IgE *in vitro* was provided by Manfredi *et al.* [20], and later by Aranda *et al.* [7^{••}], who unequivocally showed the presence of specific IgE to different quinolones using radioimmunoassay (RIA). Inhibition assays showed that results were specific and when the assay was later repeated in positive cases [7^{••}] there was a decrease in the IgE response, becoming negative in some cases, thus indicating IgE clearance.

Recently, the presence of basophil activation upon quinolone stimulation has been shown in patients with immediate reactions to quinolones, with no activation in patients tolerating these drugs [7^{••},21[•]]. To confirm that basophils were activated by specific IgE antibodies, wortmannin, a potent specific inhibitor of PI3K, an

Table 1 Classification and chemical structures of the most frequently used quinolones

Generation	Quinolone	Chemical structure
First	Cinoxacin	
	Nalidixic acid	
	Ofloxacin	
Second	Norfloxacin	
	Ciprofloxacin	
	Enoxacin	
	Levofloxacin	
Fourth	Gemifloxacin	

Generation	Quinolone	Chemical structure
	Moxifloxacin	

enzyme that is activated through the cross-linking of IgE, was used, detecting that this molecule inhibited basophil activation when stimulated with anti-IgE and with quinolones, indicating activation through IgE [7^{••}]. Furthermore, similar to the situation with RIA, a decrease in basophil activation was detected over time. All these results using RIA and basophil activation confirm that an IgE-mediated mechanism exists, at least in a group of patients.

The epitopes of the quinolone molecule recognized by IgE have not been identified, although the part of the molecule including positions C2 to C6 and the 3-carboxyl group seem to be part of the epitope [20].

Clinical symptoms

Many studies have reported allergic reactions occurring within 1 h after quinolone administration, with clinical symptoms suggesting IgE-mediated hypersensitivity, although most studies are case reports or short series [13,18,21[•],22,23[•],24–26]. Different clinical categories have been described, anaphylaxis and anaphylactic shock, and urticaria, whether or not accompanied by angioedema. All quinolones may be involved, although more recently implicated quinolones include ciprofloxacin, moxifloxacin and levofloxacin [7^{••},9,20,27,28^{••}]. The publications including larger series of patients [7^{••},9,20,27,28^{••}] are shown in Table 2.

In HIV patients, many reactions related to ciprofloxacin administration have been described [29–31]. The clinical symptoms are typically anaphylaxis and the pathophysiologic mechanisms responsible for this increase in frequency are poorly understood [32].

Diagnosis

The diagnosis of immediate hypersensitivity reactions is often difficult to accomplish, because skin testing has not proven to be reliable. Some authors consider skin testing useful [22,25–27,28^{••}] but others have shown a considerable number of false-positive results [7^{••},9,13,20,33]. These differences may be explained by the capacity of some quinolones to induce direct histamine release [7^{••}]. Table 3 shows the skin test concentrations that have been

Table 2 Type of reactions and drug involved in large series of immediate hypersensitivity reactions to quinolones

N	Reactions	Quinolones	Reference
38	Urticaria (31.6%). Anaphylaxis (42.1%) Anaphylactic shock (26.3%)	Moxifloxacin (63.2%); ciprofloxacin (28.9%) Levofloxacin (7.9%)	Aranda <i>et al.</i> [7**]
64	Urticaria (53.1%). Anaphylaxis (32.8%) Anaphylactic shock (14.1%)	Moxifloxacin (23.4%); ciprofloxacin (43.7%) Levofloxacin (12.5%) Ofloxacin (20.3%)	Seitz <i>et al.</i> [9]
55	Urticaria (85%) Anaphylactic shock (13%)	Ciprofloxacin (23.2%) Cinoxacin (23.2%) Lomefloxacin (13%) Ofloxacin (10.1%) Pipemidic acid (8.7%) Pefloxacin (8.7%) Norfloxacin (5.8%) Nalidixic acid (2.9%) Rufloxacin (2.9%) Enoxacin (1.4%)	Manfredi <i>et al.</i> [20]
16	Urticaria (% not described) Anaphylaxis (% not described)	Moxifloxacin (43.7%) Ciprofloxacin (31.2%) Ofloxacin (12.5%) Norfloxacin (6.2%) Pipemidic acid (6.2%)	Venturini <i>et al.</i> [27]
12	Urticaria (66.7%). Anaphylaxis (33.3%)	Moxifloxacin (15.4%); ciprofloxacin (38.5%) Levofloxacin (38.5%) Norfloxacin (8.3%)	Lobera <i>et al.</i> [28**]

recommended by some authors, although others were unable to establish a nonirritant concentration for intra-dermal testing [9,21*,22,23*,25,26,28**,33].

With regard to in-vitro tests, RIA and basophil activation test (BAT) have been used with promising results. Two studies have been published using RIA in patients with immediate reactions to quinolones and, although the specificity in both was 100%, one found 54.5% positive results [20] and the other 28.9% [7**]. Both studies used the same in-vitro methodology and clinical approach for patient selection, and had a short interval between the reaction and the test, although the quinolone involved

and the type of reaction differed. In the first study [20], the most frequent reaction was urticaria (85%), with just 13% of cases having anaphylactic shock, and the drugs most frequently involved were ciprofloxacin (23%) and cinoxacin (23%). In the second study [7**], two-thirds of the cases developed severe reactions, with the drugs most frequently involved being moxifloxacin (63.2%) and ciprofloxacin (28.9%).

With regard to BAT, preliminary studies, performed with fewer cases, have shown contradictory results [9,21*,28**]. Two of the studies performed BAT using CD63; the first study in four patients with anaphylaxis

Table 3 Nonirritant concentrations of the most common quinolones for use in skin prick and intradermal testing

Quinolone	Concentration prick	Concentration ID	Pat/Con	References
Moxifloxacin	4 mg/ml	0.004 mg/ml	1/10	Sánchez-Morillas <i>et al.</i> [25]
	5 mg/ml	0.005 mg/ml	5/nd	Ben Said <i>et al.</i> [21*]
	1–20 mg/ml	Not done	1/5	González-Mancebo <i>et al.</i> [22]
	Not done	0.005–0.05 mg/ml	3/nd	Chang <i>et al.</i> [23*]
	1.6 mg/ml	Not achieved	19/nd	Seitz <i>et al.</i> [9]
Ciprofloxacin	1 mg/ml	0.001–0.01 mg/ml	1/10	Sánchez-Morillas <i>et al.</i> [25]
	1 mg/ml	0.001 mg/ml	1/5	González-Mancebo <i>et al.</i> [22]
	Not done	0.005–0.05 mg/ml	3/nd	Chang <i>et al.</i> [23*]
	2 mg/ml	Not achieved	19/nd	Seitz <i>et al.</i> [9]
	0.02 mg/ml	0.02 mg/ml	6/10	González <i>et al.</i> [26]
	0.02 mg/ml	0.02 mg/ml	12/10	Lobera <i>et al.</i> [28**]
	Not achieved	Not achieved	0/25	Empedrad <i>et al.</i> [33]
	5 mg/ml	0.005–0.05 mg/ml	1/10	Sánchez-Morillas <i>et al.</i> [25]
Levofloxacin	5 mg/ml	0.005 mg/ml	5/nd	Ben Said <i>et al.</i> [21*]
	1–10 mg/ml	Not done	1/5	González-Mancebo <i>et al.</i> [22]
	Not done	0.005–0.05 mg/ml	3/nd	Chang <i>et al.</i> [23*]
	5 mg/ml	Not achieved	19/nd	Seitz <i>et al.</i> [9]
	5 mg/ml	0.05 mg/ml	6/10	González <i>et al.</i> [26]
	5 mg/ml	0.05 mg/ml	12/10	Lobera <i>et al.</i> [28**]
	0.025 mg/ml	0.025 mg/ml	0/25	Empedrad <i>et al.</i> [33]

nd, not described.

symptoms after a drug provocation test (DPT) [9,28**] and the second study in six cases diagnosed by skin testing or DPT, detecting no significant activation of basophils using different quinolones. Another study [21*] evaluated five cases with anaphylaxis induced by quinolones and who were skin-test-positive, using CD203c as the activation marker in the BAT, with positive results in all cases and negative results in all controls, pointing out the usefulness of BAT for diagnosis.

Our group has recently evaluated a larger group of patients with immediate reactions using BAT with CD63 as the basophil activation marker, and found an overall positivity of 71.05%, which doubled the sensitivity detected with RIA, with no improvement in sensitivity when results from both methods were combined [7**]. Moreover, BAT was positive in 69% of the cases with severe reactions, which is important as it enables DPT to be avoided for diagnosis.

Drug provocation test has been widely used in the diagnosis of patients with immediate reactions to quinolones [7**,9,13,21*,22,23*,25–27,28**], although this procedure is not free of risk since immediate reactions can be severe. It is done in a single-blind, placebo-controlled manner under strict hospital surveillance with quinolones at the concentrations recommended [7**,9], as shown in Table 4.

Drug provocation test is used to establish a diagnosis in skin-test-negative cases, to choose an alternative quinolone, or to evaluate for cross-reactivity in patients who are skin-test or in-vitro test positive. However, an important indication for DPT is confirmation of tolerance, as a recent study [9] showed that only 11.8% of patients with a clear history of immediate reactions to quinolones who underwent DPT were in fact positive. Therefore, in this study the diagnosis of allergy was ruled out in nearly 90% of patients evaluated, indicating that the clinical history alone is a vague and unreliable indicator of true quinolone hypersensitivity. In addition, Venturini *et al.* [27] performed DPT in patients with either positive or negative skin tests and detected that only 5% of patients with negative skin tests had a positive DPT, whereas 50% of the patients with positive skin tests had a positive DPT. All the positive DPT consisted of urticaria and responded rapidly to antihistamines. This shows that skin testing

can produce false positive results and also that DPT is the gold standard [27].

Nonimmediate reactions

The new advances regarding underlying immunological mechanisms, clinical symptoms and diagnosis of non-immediate reactions are described below.

Mechanisms involved

Few studies have been done regarding the mechanisms underlying nonimmediate reactions to quinolones. Schmid *et al.* [8] showed that these reactions can be associated with a strong T-cell immune response against the relevant quinolone, providing evidence that the original compound was recognized by T cells without the necessity of drug metabolism or processing.

Quinolones can bind covalently to proteins upon ultraviolet A exposure, thus initiating immunological reactions, since dendritic cells are photomodified and therefore induce photoallergy. The piperazinyl ring at position 7 is the most probable protein-photobinding site [34].

Clinical symptoms

Nonimmediate hypersensitivity reactions to quinolones are less frequent than immediate hypersensitivity reactions. Maculopapular exanthema, fixed drug eruptions and photoallergy are the more commonly reported reactions. There were reports of AGEP and more severe reactions such as SJS and TEN. Most nonimmediate reactions were published as case reports [10–16].

Schmid *et al.* [8] described six patients with nonimmediate reactions: four exanthemas and two AGEP; induced by ciprofloxacin in four, moxifloxacin in one and ciprofloxacin and norfloxacin in one case. Later, Seitz *et al.* [9] reported a group of 37 patients with a history of non-immediate reactions to quinolones: 29 with maculopapular exanthema, seven with fixed drug eruption and one with AGEP, induced by ciprofloxacin in 17 cases, ofloxacin in 6, levofloxacin in 8 and moxifloxacin in 6. Venturini *et al.* [27] evaluated 10 patients with maculopapular exanthema and delayed urticaria, and the drugs involved in the reaction were ciprofloxacin in four, norfloxacin in three, ofloxacin in one, moxifloxacin in one and pipemidic acid in one.

Diagnosis

As with immediate reactions, the role of patch or intradermal testing has had contradictory results. Some authors have found positive patch tests in 50% of non-immediate reactions [8], whereas others found no positive results [9]. Regarding intradermal tests, 80% positivity has been reported, though the possibility of an irritant response was not ruled out [27].

Table 4 Drug doses recommended for drug provocation testing with quinolones

	Doses of the quinolones (mg)			
	Ofloxacin	Ciprofloxacin	Levofloxacin	Moxifloxacin
First	5	5	5	5
Second	25	50	50	50
Third	50	100	100	100
Fourth	100	150	150	100
Fifth	200	200	200	150

Patch testing has been done using fluoroquinolone tablets (250 mg ciprofloxacin, 200 mg ofloxacin, 250 mg levofloxacin, and 400 mg moxifloxacin) ground in a mortar and suspended with 1 ml of saline [8,9]. Intradermal tests with delayed readings have been done with the same approach as used in immediate skin testing [27].

Lymphocyte transformation tests have also been used in the diagnosis, with authors detecting proliferation to ciprofloxacin and moxifloxacin in all six cases evaluated with nonimmediate reactions, with no proliferation in controls [8].

From the results of Seitz *et al.* [9], and similar to what happens in patients who are allergic to penicillins [35], it, however, seems clear that DPT is the most reliable test for diagnosing nonimmediate reactions to quinolones. The authors performed DPT in patients with nonimmediate reactions and found just 7% to be positive, with all being skin-test-negative. Venturini *et al.* [27] described 30% of positive DPT in cases with nonimmediate reactions, being all mild reactions.

Cross-reactivity

Cross-reactivity in immediate hypersensitivity reactions to quinolones has received more attention. One of the first studies evaluated three patients using DPT, with one case reacting to norfloxacin and nalidixic acid, another to ciprofloxacin and pipemidic acid and the third to pipemidic and nalidixic acid with good tolerance to norfloxacin [18]. These first results seem to indicate an important degree of cross-reactivity between first and second-generation quinolones.

Analysis of cross-reactivity in the newer quinolones, such as moxifloxacin, however, suggests that it is lower. Sánchez-Morillas *et al.* [25] described one patient with anaphylaxis after moxifloxacin administration and good tolerance to levofloxacin; Chang *et al.* [23•] reported three patients with urticaria or anaphylaxis with moxifloxacin, and good tolerance was found in the two tested with ciprofloxacin. González *et al.* [26] evaluated three cases with immediate hypersensitivity to moxifloxacin, among whom one tolerated ciprofloxacin, one tolerated ciprofloxacin and levofloxacin and one developed an immediate hypersensitivity reaction to ciprofloxacin. This seems to indicate that many cases with immediate hypersensitivity reactions to moxifloxacin may tolerate ciprofloxacin and even levofloxacin. However, when these same authors evaluated cross-reactivity in three patients with immediate hypersensitivity reactions to ciprofloxacin, all reacted to moxifloxacin and one also to levofloxacin, indicating that cross-reactivity is not a bilateral phenomenon.

Regarding levofloxacin, some authors have suggested a low degree of cross-reactivity, with four out of five cases

with immediate hypersensitivity reactions to ciprofloxacin tolerating levofloxacin and three out of four allergic to levofloxacin tolerating ciprofloxacin [28••]. This shows the difficulty of the situation and there is no general rule to predict cross-reactivity among different quinolones.

In-vitro studies in both immediate [7••,20] and nonimmediate [8] reactions to quinolones are difficult to interpret and can overestimate cross-reactivity. Investigations of T-cell clones [8] of patients with maculopapular exanthema to ciprofloxacin showed that sensitization can be exclusively to ciprofloxacin, or to two or more quinolones.

Finally, in the particular case of photoallergic reactions, cross-reactivity among six fluoroquinolones has been demonstrated using a murine model, suggesting the presence of a common epitope (probably the piperazinyl ring at position 7 present in several fluoroquinolones) recognized by fluoroquinolone-specific T cells [36].

Conclusion

Allergic reactions to quinolones have increased over the past decade, particularly reactions that are IgE-mediated and induced by moxifloxacin. The diagnosis is complex because skin testing can be irritant and induce false-positive results. Therefore, in many cases the only way to diagnose tolerance is with DPT, which is not itself free of risk. Promising results using RIA and BAT have recently been published and they may become helpful to improve diagnosis. Nonimmediate reactions have also been described, though they are less frequent and with a demonstrated T-cell mechanism. The pattern of cross-reactivity is complex and difficult to predict.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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