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TITLE: Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved

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ABSTRACT

Background: Hypersensitivity reactions to fluoroquinolones seem to be on the increase, especially immediate type reactions.

Objective: The aim of this study was to determine whether several conditions, including gender, age, type of reaction, time interval between the reaction and the study, type of symptoms, the specific fluoroquinolone involved in the reaction and previous confirmed hypersensitivity to betalactams or to other drugs were factors contributing to the development of hypersensitivity to fluoroquinolones.

Method: We analyzed retrospectively all patients attending our allergy department between January 2005 and December 2010 because of a reaction associated with fluoroquinolone administration. The diagnosis was confirmed by basophil activation test or drug provocation tests. In accordance with the results, patients were then classified as having hypersensitivity or non-hypersensitivity to fluoroquinolones.

Results: A group of 218 patients was evaluated; 69 were confirmed as having hypersensitivity, 146 as non-hypersensitivity and 3 were excluded. Comparisons between groups showed that the allergic patients more often had a previous confirmed hypersensitivity to betalactams (P=0.029), immediate reactions (P=0.001), and anaphylaxis (P=0.000), and moxifloxacin was the fluoroquinolone most frequently involved (P=0.027). The logistic regression analysis showed

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three factors associated with the diagnosis of hypersensitivity reactions to fluoroquinolones: previous hypersensitivity to betalactams (OR: 4.571; 95% CI: 0.987-21.171; adjOR: 23.654; 95% CI: 1.529-365.853), immediate reactions (OR: 17.333; 95% CI: 4.374-68.691; adjOR: 52.493; 95% CI: 6.621-416.200),and reactions induced by moxifloxacin (OR: 3.091; 95% CI: 1.160-8.239; adjOR: 13.610; 95% CI: 2.419-76.565),

Conclusion: In patients who develop reactions to fluoroquinolones, hypersensitivity is more often confirmed in those with immediate reactions and when moxifloxacin is involved. Moreover, patients with hypersensitivity to betalactams are more prone to developing hypersensitivity reactions to fluoroquinolones.

KEYWORDS

Allergy, penicillin, fluoroquinolones, IgE, anaphylaxis.

ABBREVIATIONS

AGEP: acute generalized exanthematic pustulosis.

SJS: Stevens-Johnson syndrome.

TEN: Toxic epidermal necrolysis.

BAT: Basophil activation test.

DPT: Drug provocation test.

SI: Stimulation index

ENDA: European Network for Drug Allergy

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INTRODUCTION

Consumption of fluoroquinolones has increased over the years, particularly certain derivatives like ciprofloxacin, levofloxacin and more recently moxifloxacin (1). In parallel, the frequency of hypersensitivity reactions to these drugs also seems to have increased in the past decade, with the result that fluoroquinolones are now probably the non-betalactam antibiotic most frequently involved in allergic drug reactions (2). Fluoroquinolones can induce hypersensitivity reactions by several mechanisms, mostly IgE and T-cell dependent reactions, with most hypersensitivity reactions being of the IgE type, such as urticaria and anaphylaxis (3-8). T-cell dependent reactions have been reported less often and include maculopapular exanthema (5,9), fixed drug eruptions (10-12), acute generalized exanthematic pustulosis (AGEP) (9), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (13-15).

Based on spontaneous reports of anaphylaxis induced by fluoroquinolones, an increase has been reported in a German population in the total number of cases of anaphylaxis since 2000, mainly due to reactions induced by moxifloxacin (3). These results are supported by studies recently carried out in Spain in a large group of patients with immediate hypersensitivity reactions to fluoroquinolones, in which moxifloxacin was involved in 63.2% of the cases, followed by ciprofloxacin in 28.9% and levofloxacin in 7.9% (4). The reasons influencing the increase in moxifloxacin hypersensitivity reactions in countries where it is prescribed, such as Germany (3) and Spain (4,7,16), have not been identified. The basic chemical structure of fluoroquinolones consists of a bicyclic skeleton, formed by one pyridone and another aromatic ring, containing a fluorine atom attached at position C-6. In some cases a second halogen substituent is present at

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position C-8. Structural differences between fluoroquinolones are derived from the substituent at positions N-1, C-7 and C-8 (17) (Figure 1). Although most fluoroquinolones are not fully metabolized, they are partly metabolized as reactive intermediates through mechanisms such as glucuronidation on the carboxy group at C-3, or oxidation or sulphation on the piperazine ring at C-7 (18,19). These metabolites may react with proteins forming covalent hapten-protein conjugates capable of interacting with the immune system (20). Whether differences in the chemical structures or their metabolites can have a role in the increase in reactions to some particular fluoroquinolones is at present unknown. Nor has it been determined whether other conditions such as hypersensitivity to other antibiotics can occur, an association known as "multiple drug allergy syndrome" (21-24).

The diagnosis of immediate hypersensitivity reactions is often difficult because skin testing is not reliable; while some authors consider skin testing useful (7,16,25-27), most studies have reported a high number of false-positive results (5,6,28,29). These differences may be explained by the capacity of some fluoroquinolones to induce direct histamine release (5,16). Recently, *in vitro* approaches, such as radioimmunoassay and the basophil activation test (BAT), have proved useful tools for diagnosis, although their sensitivity is not optimal (4,6,30,31). As a result, often the only method available to establish the diagnosis is the drug provocation test (DPT), a procedure that is not free of risk (4,6,8).

The aim of this study was to identify whether certain conditions such as gender, age, a previous confirmed allergy to betalactams or to other drugs, as well as the type of reaction, the time interval between the reaction and the study, type of symptoms and the specific fluoroquinolone

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involved in the reaction were factors contributing to the development of hypersensitivity to fluoroquinolones.

METHODS

Patients

This retrospective study was undertaken with patients who required evaluation for the first time at our allergology department because of a history suggestive of hypersensitivity reactions to a fluoroquinolone derivative over a period of 6 years (January 2005 to December 2010). The work-up procedure was the same throughout the whole evaluation period, with no relevant modifications, and consisted of a detailed clinical history (32), BAT and, if necessary a DPT. Skin testing was not performed because of its reported low sensitivity and specificity (4,6,8).

As a working classification, patients were grouped into those with immediate reactions (reactions appearing within one hour after fluoroquinolone administration) and those with non-immediate reactions (reactions appearing after one hour). In the group with immediate reactions different clinical categories were established: anaphylaxis and anaphylactic shock, defined according to the criteria of Sampson (33); and urticaria when the manifestations were limited to the skin and consisted of pruritic, erythematous cutaneous elevations that blanched with pressure at various sites on the body. BAT was done in all patients with immediate reactions and, if negative, DPT was performed to confirm the diagnosis. In the group with non-immediate reactions, the categories included were maculopapular and urticarial exanthemas and severe reactions such as AGEP, SJS and TEN. The former were diagnosed by DPT and the latter severe reactions by the clinical history. After completing the allergological evaluation patients were classified as having hypersensitivity or non-hypersensitivity to fluoroquinolones.

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The study was conducted according to the principles of the Declaration of Helsinki and approved by the hospital Ethics Committee (FIS PI 11/01416). All the participants were informed orally about the study and signed the corresponding informed consent.

Basophil activation test

The BAT was performed with the following fluoroquinolones: norfloxacin (Norfloxacino cinfa), ciprofloxacin (Ciprofloxacino Normon, Madrid, Spain), moxifloxacin (Actira, Bayer, Barcelona, Spain) and levofloxacin (Tavanic, Sanofi-Avantis, Barcelona, Spain) as previously described by our group (4). The two optimal concentrations for each fluoroquinolone (norfloxacin: 2 and 0.2 mg/ml; ciprofloxacin: 2 and 0.2 mg/ml; moxifloxacin: 0.2 and 0.1 mg/ml; levofloxacin: 4 and 2 mg/ml) were chosen based on dose-response curves and cytotoxicity studies. The cells were analyzed in a FACSCalibur flow cytometer (Becton Dickinson, San Jose, CA) by acquiring at least 1000 basophils per sample and results were considered positive when the stimulation index (SI), calculated as the ratio between the percentage of degranulated basophils with the different drugs and the negative control, was 3 at at least one of the concentrations used.

Drug provocation test

This was performed in a single blind procedure under strict hospital surveillance, following the European Network of Drug Allergy (ENDA) recommendations (34). On the first day, placebo capsules were given at different times. On the second day (at least 1 week later) increasing doses of the suspected fluoroquinolone were administered orally at intervals of 30 min until reaching the full therapeutic dose or until symptoms of a drug reaction occurred (see Table 1). The fluoroquinolones used were norfloxacin (Norfloxacino cinfa), ciprofloxacin (Ciprofloxacino

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Normon), moxifloxacin (Actira) or levofloxacin (Tavanic). If cutaneous and/or respiratory symptoms or changes in vital signs (rhythm alterations, decrease in peak expiratory flow rate or hypotension) appeared, the procedure was stopped and the symptoms were evaluated and treated. If good tolerance occurred, a therapeutic course of 2 days was given 24-h afterwards. All the drugs and placebo were given in opaque capsules prepared by the hospital pharmacy service.

Statistical analysis

The following variables were analyzed: confirmed allergy to betalactams (patients with a compatible history of betalactam allergy confirmed by a positive skin test, in vitro tests (BAT or radioimmunoassay) or DPT previous to the reaction with the quinolone), type of reaction (immediate, in those appearing within 1 hour after drug intake, and non-immediate in those appearing more than one hour after drug intake), fluoroquinolone involved in the reaction (ciprofloxacin, moxifloxacin, levofloxacin, norfloxacin, or non-identified), gender, age, confirmed allergy to other drugs (patients with a compatible history of drug allergy to a non-betalactam drug confirmed by a positive skin test or DPT previous to the reaction with the quinolone), time interval between the reaction and the study in days, and type of symptoms (cutaneous, anaphylaxis, and non-identified).

Comparisons for quantitative variables without normal distributions were made by the Mann-Whitney tests and between qualitative variables by the chi-square test. All reported P values represented two-tailed tests, with values <0.05 considered statistically significant. A logistic regression analysis was performed to establish those characteristics that were associated with a diagnosis of allergy to fluoroquinolones.

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RESULTS

We studied a group of 218 patients with a clinical history indicative of hypersensitivity reactions to fluoroquinolones over a six-year period (2005-2010). Some information about these patients has been published recently (2). Of the 218, 142 (65.14%) were female, 24 (11.11%) had been diagnosed as having hypersensitivity to betalactams and 46 (21.1%) to other drugs before developing any reaction to fluoroquinolones. Their median age was 51 (IR: 37-64) years and the median time interval between the reaction and the study was 180 (IR: 60-360) days. According to the clinical records and the description given by the patients the type of reaction was immediate in 152 (69.72%) cases and non-immediate in 66 (30.28%) cases. The drugs involved in the reactions were ciprofloxacin in 127 (58.26%) cases, moxifloxacin in 62 (28.44%), levofloxacin in 12 (5.5%), norfloxacin in 13 (5.96%), and non-identified fluoroquinolones in 4 (1.83%). The clinical symptoms were cutaneous (urticarial or exanthema) in 119 (54.59%) cases, anaphylaxis or anaphylactic shock in 59 (27.06%), and not well defined in 40 (18.35%).

The absolute number of patients evaluated because of a history of hypersensitivity to fluoroquinolones significantly increased over the years, with 10 patients in 2005, 24 in 2006, 35 in 2007, 39 in 2008, 48 in 2009 and 62 in 2010 (Figure 2). After completing the allergological work-up 3 patients were excluded (1 anaphylactic shock and 2 anaphylaxis) because the diagnosis was not confirmed (2 did not give consent for DPT and 1 due to risk factors) and 215 were finally included. Among them, 69 (32.1%) patients were classified as having hypersensitivity: 66 (95.65%) with immediate reactions and 3 (4.54%) with non-immediate reactions. The absolute number of patients with confirmed hypersensitivity was significantly increased over the time: 1 in 2005, 2 in 2006, 8 in 2007, 10 in 2008, 22 in 2009, and 29 in 2010

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(Figure 2). The clinical symptoms and the techniques used to confirm the diagnosis in those with hypersensitivity to fluoroquinolones are shown in Figure 3 and the description of the DPT in patients with immediate and non-imediate reactions is shown in Table 2. Regarding those finally confirmed as not hypersensitive, 83 had symptoms compatible with immediate reactions (12 anaphylaxis, 48 urticaria and in 23 although patients identified reactions as immediate, the symptoms were non-identified) and 63 with non immediate (31 exanthemas, 15 urticarias and 17 non-identified).

Table 3 shows the clinical and demographic characteristics of the patients who did or did not have hypersensitivity to fluoroquinolones after establishing the diagnosis. Comparisons between the two groups showed significant differences for the presence of previous hypersensitivity to betalactams, type of reaction, the specific fluoroquinolone involved and the symptoms presented. In fact, in those confirmed as having hypersensitivity the percentage of subjects previously diagnosed as having hypersensitivity to betalactams (23.19%) was four times higher than those who were not allergic (5.48%). Analyzing those cases with confirmed hypersensitivity to betalactams, we found that all had immediate hypersensitivity reactions, previously diagnosed by skin testing in 67% and by DPT in 33%, and that amoxicillin was the drug most frequently involved (73%). Also, in those finally confirmed as having hypersensitivity to fluoroquinolones, the percentage of immediate reactions was two times higher, with anaphylaxis and anaphylactic shock being nearly eight times higher than in those finally confirmed as non-allergic. Finally, the percentage of cases in whom moxifloxacin was the culprit drug was more than two times higher in those finally confirmed as having hypersensitivity (47.83%) than in those who were not allergic (19.18%).

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Concerning hypersensitivity to non-betalactam drugs, no differences were found in their frequency between those with (15.94%) and those without fluoroquinolone hypersensitivity (23.97%). In those with hypersensitivity to non-betalactam drugs, 81% had idiosyncratic reactions to NSAIDs diagnosed by DPT, 12% had non-immediate reactions to radio contrast media diagnosed by skin testing or DPT, and the rest had immediate allergy to anesthetics and pyrazolones diagnosed by skin testing. No differences were found in age, gender or time interval from reaction to study between those with or without hypersensitivity to fluoroquinolones.

The logistic regression analysis showed three factors associated with the development of hypersensitivity reactions to fluoroquinolones (Table 4): previous hypersensitivity to betalactams (OR: 4.571; 95% CI: 0.987-21.171; adjOR: 23.654; 95% CI: 1.529-365.853), immediate reactions (OR: 17.333; 95% CI: 4.374-68.691; adjOR: 52.493; 95% CI: 6.621-416.200),and reactions induced by moxifloxacin (OR: 3.091; 95% CI: 1.160-8.239; adjOR: 13.610; 95% CI: 2.419-76.565). No interaction was detected between any of the variables studied.

DISCUSSION

The data reported here support previous evidence indicating that allergy to fluoroquinolones may be on the increase (2-4). First, we detected an increase in the number of patients evaluated over the years with a clinical history compatible with a hypersensitivity reaction to fluoroquinolones, even when correcting for the total number of patients evaluated with a clinical history of drug hypersensitivity per year, as we have reported previously (2). Second, we detected an increase in the percentage of patients finally confirmed as having hypersensitivity, even though we used the same allergological work-up during the whole six-year period. This could be explained by the

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increased consumption of fluoroquinolones (1) and the introduction onto the market of moxifloxacin (3,4,7,16). In fact, in Spain the consumption of antibiotics in 2009 was 62.6% penicillins, followed by fluoroquinolones (12.2%). From 1992 to 2009 the use of fluoroquinolones remained stable, with ciprofloxacin representing 50%, but since levofloxacin and moxifloxacin were introduced in the market in 1998 and 2000 respectively there has been an increase in the consumption of these drugs, accounting for 26% and 15% respectively (35). Nevertheless, other factors may also be influencing these results.

Of all the patients evaluated, we finally confirmed 32% as having hypersensitivity, with 68% of the cases tolerating the administration of fluoroquinolones. Interestingly, Seitz et al showed that 70% of cases with a clinical history of fluoroquinolone hypersensitivity were finally shown not to have hypersensitiviy (5). Thus, this study and ours both indicate that the clinical history is not reliable when evaluating hypersensitivity reactions to fluoroquinolones. This lack of reliability is particularly relevant in patients with non-immediate reactions, where fewer than 5% of cases evaluated were finally confirmed as having hypersensitivity, as occurred with non-immediate reactions to betalactams in adults (36) and children (37,38), where most patients with urticarial or exanthematic reactions tolerated betalactam administration.

Nearly 70% of the immediate hypersensitivity reactions were either anaphylaxis or anaphylactic shock, confirming previous reports that immediate reactions to fluoroquinolones can be severe (3,4). BAT was done in all the patients with immediate reactions, with a diagnosis being achieved in 36% of the cases, who therefore did not need DPT; this confirms previous results (4,30). This is important if we consider that 24% had anaphylactic shock and 42% anaphylaxis.

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On the other hand, all the patients with non-immediate reactions experienced moderate exanthemas and were diagnosed by DPT, with results similar to those reported by others for fluoroquinolones (5) and betalactams (35-37).

Comparison of those cases finally confirmed as having hypersensitivity with those with good tolerance showed that patients were more likely to be confirmed as having hypersensitivity when moxifloxacin was the culprit fluoroquinolone and the reaction appeared within one hour after drug administration. These results support previous data suggesting an increase in fluoroquinolone anaphylaxis, mainly due to moxifloxacin (3), and other results showing that in a group of patients with immediate hypersensitivity reactions to fluoroquinolones moxifloxacin induced more severe reactions, with 75% having anaphylaxis versus 54% in reactions induced by ciprofloxacin (4).

This difference between the fluoroquinolones could be linked to the chemical structure of moxifloxacin. The immunoreactivity of fluoroquinolones may be related to their ability to conjugate to proteins, which is possible in ciprofloxacin, levofloxacin and moxifloxacin by the formation of the corresponding glucuronides at position 3 (19). However, though they possess the same basic structure, the three fluoroquinolones differ in substituents at N-1, C-7 and C-8, which may be the key factor in the formation of the relevant immunogenic adducts. The aminoheterocyclic moieties at C-7 appear to be the major target for biotransformation, which can be modulated by substituents of the ring, and the corresponding structure after metabolism seems to be involved in the formation of the adducts. In fact, there is more metabolism caused by the diazabicyclic ring at C-7 in moxifloxacin compared to that caused by piperazine or a methyl

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modified piperazine moiety at C-7 in ciprofloxacin and levofloxacin, respectively (18,19). This pattern of reactivity could explain the immune behavior we detected.

Although in our study the number of patients previously sensitized to betalactams was low, these subjects were more likely to be diagnosed as having hypersensitivity to fluoroquinolones. The association between allergy to betalactams and other antibiotics was referred to as a multiple drug allergy syndrome by Sullivan et al (21). These authors reported that 21% of patients with immediate allergic reactions to penicillin later developed allergic reactions to non-betalactam antibiotics compared with just 1% of those who were non-allergic to penicillins (21). Although the authors did not provide detailed information to enable further analysis, they suggested that the response to different antibiotics not chemically related could be due to an alteration in the immune response to haptens. However, another study was unable to confirm this suggestion (22). Also, a large observational study showed that patients with a history of allergy to sulfonamide antibiotics had an increased risk of an allergic reaction to non-antibiotic sulfonamides, specially to penicillin, compared with those without such a history. These authors suggest that this association is probably attributable to a predisposition to allergic reactions rather than to cross-reactivity (23). Since then, the only studies published concern non-immediate drug reactions, with the authors suggesting that in delayed type hypersensitivity reactions a massive immune stimulation occurs and that it is this condition that represents a risk factor for further drug hypersensitivity (24). In our study we found that patients with hypersensitivity to fluoroquinolones were likely to have been previously diagnosed as allergic to betalactams. In fact, the reactions were IgE mediated in both fluoroquinolone and betalactam allergies. Although the reasons remain unknown, the fact that patients who are allergic to betalactams are more

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likely to be prescribed fluoroquinolones than those who are not allergic to betalactams may be one explanation, in addition to a genetic predisposition. However, no association was detected between allergy to fluoroquinolones and allergy to non-betalactam drugs, where non-IgE mechanisms were more frequent, or even to some NSAIDs, where clear IgE selective responses have been reported.

In conclusion, hypersensitivity reactions to fluoroquinolones seem to have increased, particularly immediate type reactions, induced by moxifloxacin and in patients previously diagnosed with hypersensitivity to betalactams. These results need to be confirmed in larger populations by further appropriately designed prospective studies.

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Table 1. Incremental doses of the fluoroquinolones used in the drug provocation test.

	Doses of the fluoroquinolone (mg)			
	Norfloxacin	**Ciprofloxacin**	**Levofloxacin**	**Moxifloxacin**
First	5	5	5	5
Second	50	50	50	50
Third	100	100	100	100
Fourth	100	150	150	100
Fifth	150	200	200	150

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Table 2. Results of the drug provocation test in immediate and non-immediate reactions.

	Immediate	Non Immediate
Positive DPT (N)	42	3
Fluoroquinolones (N,%)		
Ciprofloxacin	17 (40.48%)	3 (100%)
Moxifloxacin	22 (52.38%)	0 (0%)
Levofloxacin	2 (4.76%)	0 (0%)
Norfloxacin	1 (2.38%)	0 (0%)
Symptoms		
Anaphylaxis	27 (64.29%)	0 (0%)
Urticaria	15 (35.71%)	2 (66.67%)
Exanthema	0 (0%)	1 (33.33%)
Time interval (minutes, median, IR)	30 (10-50)	1440 (600-4320)
Cumulative dose (mg, median, IR)	305 (155-355)	505 (505-505)

Table 3. Clinical and demographic characteristics of the patients evaluated. Comparisons between those with hypersensitivity and non hypersensitivity reactions.

	Hypersensitivity	**Non hypersensitivity**	**P**
Total number, N (%)	69 (32.1%)	146 (67.9%)	
Age (years)*	51 (37-64)	50 (34-63)	0.386
Gender (female), N (%)	47 (68.12%)	93 (63.70%)	0.658
Allergy to betalactams (yes), N (%)	16 (23.19%)	8 (5.48%)	**0.029**
Allergy to other drugs (yes), N (%)	11 (15.94%)	35 (23.97%)	0.293
Time interval reaction-study (days)*	180 (90-330)	152 (60-360)	0.722
Type of reaction, N (%)			**0.000**
Immediate	66 (95.65%)	83 (56.85%)	
Non-immediate	3 (4.35%)	63 (43.15%)	
Drug involved, N (%)			**0.027**
Ciprofloxacin	31 (44.93%)	94 (64.38%)	
Moxifloxacin	33 (47.83%)	28 (19.18%)	
Levofloxacin	4 (5.80%)	8 (5.48%)	
Norfloxacin	1 (1.45%)	12 (8.22%)	
Non-identified fluoroquinolones	0 (0%)	4 (2.74%)	
Symptoms, N (%)			**0.000**
Cutaneous	25 (36.23%)	94 (64.38%)	
Anaphylaxis	44 (63.77%)	12 (8.22%)	
Non-identified	0 (0%)	40 (27.40%)	

* Results expressed as median and interquartile range

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Table 4. Logistic regression analysis performed by stepwise backward elimination.

RISK FACTOR	BIVARIATE		MULTIVARIATE	
	OR (95% CI)	P	Adjusted OR (95% CI)	P
Hypersensitivity to BL (yes)	4.571 (0.987-21.171)	**0.049**	23.654 (1.529-365.853)	**0.024**
Immediate reaction	17.333 (4.374-68.691)	**0.001**	52.493 (6.621-416.200)	**0.001**
Moxifloxacin	3.091 (1.160-8.239)	**0.024**	13.610 (2.419-76.565)	**0.003**

BL: Betalactam, OR: Odds ratio.

LEGENDS TO FIGURES

Figure 1. General chemical structure of fluoroquinolones, ciprofloxacin, levofloxacin and moxifloxacin.

Figure 2. Number of patients evaluated with a history of hypersensitivity reactions to fluoroquinolones and with confirmed hypersensitivity reactions to fluoroquinolones from 2005 to 2010.

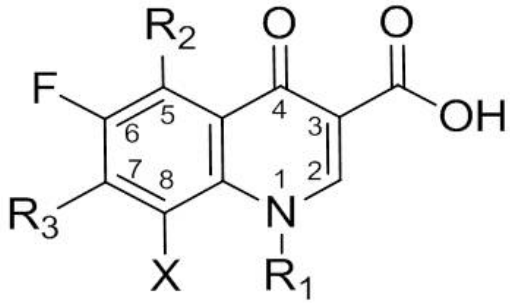
Figure 3. Clinical symptoms and diagnostic methods used for confirming the diagnosis in patients confirmed as allergic to fluoroquinolones with immediate and non-immediate reactions. MP: maculopapular; BAT: Basophil activation test; DPT: Drug provocation test.

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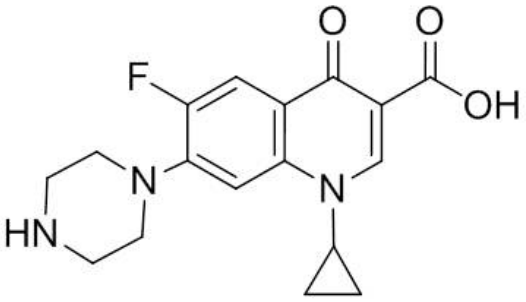
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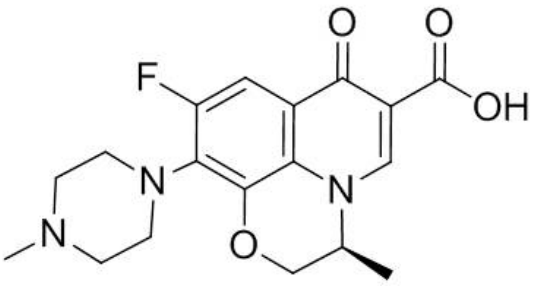
Figure 1



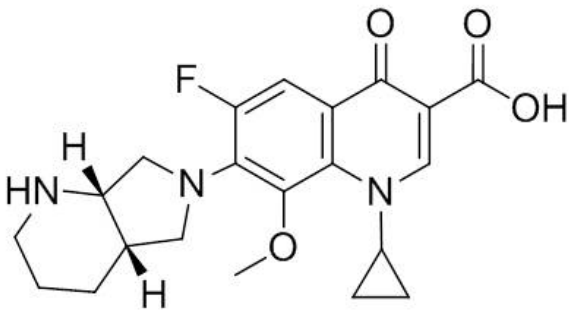
FLUOROQUINOLONES



CIPROFLOXACIN



LEVOFLOXACIN

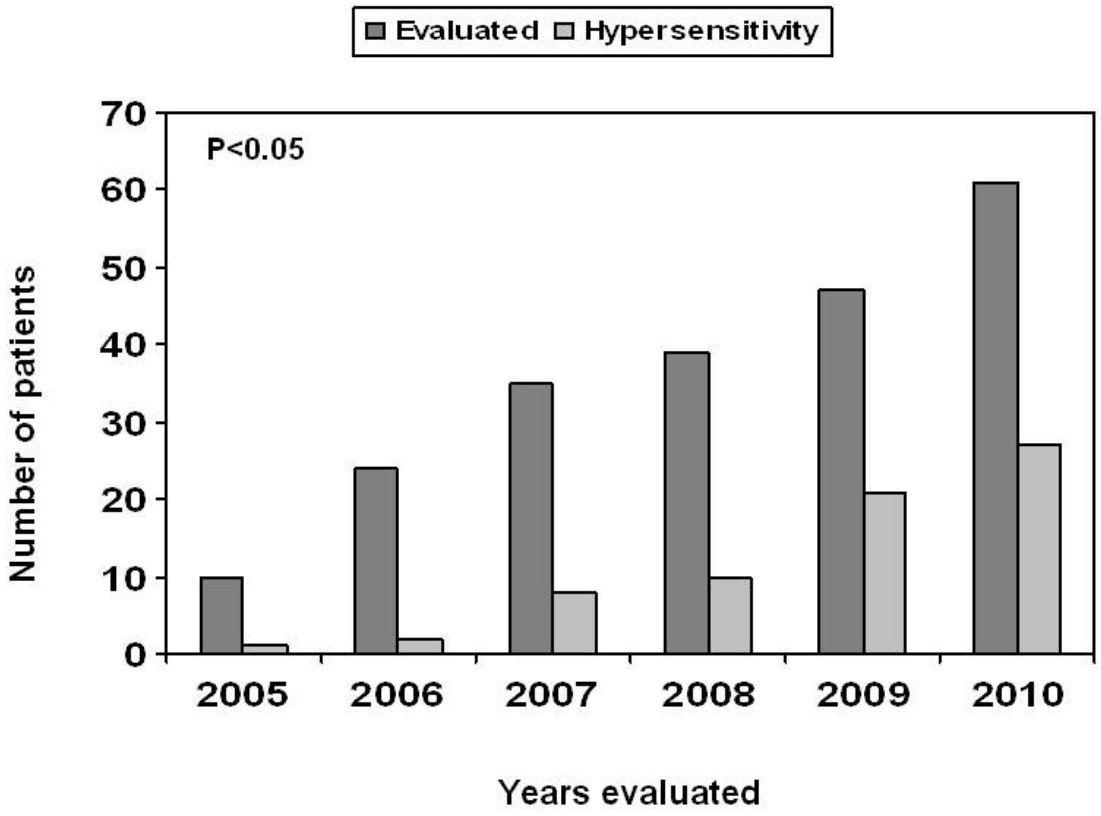


MOXIFLOXACIN

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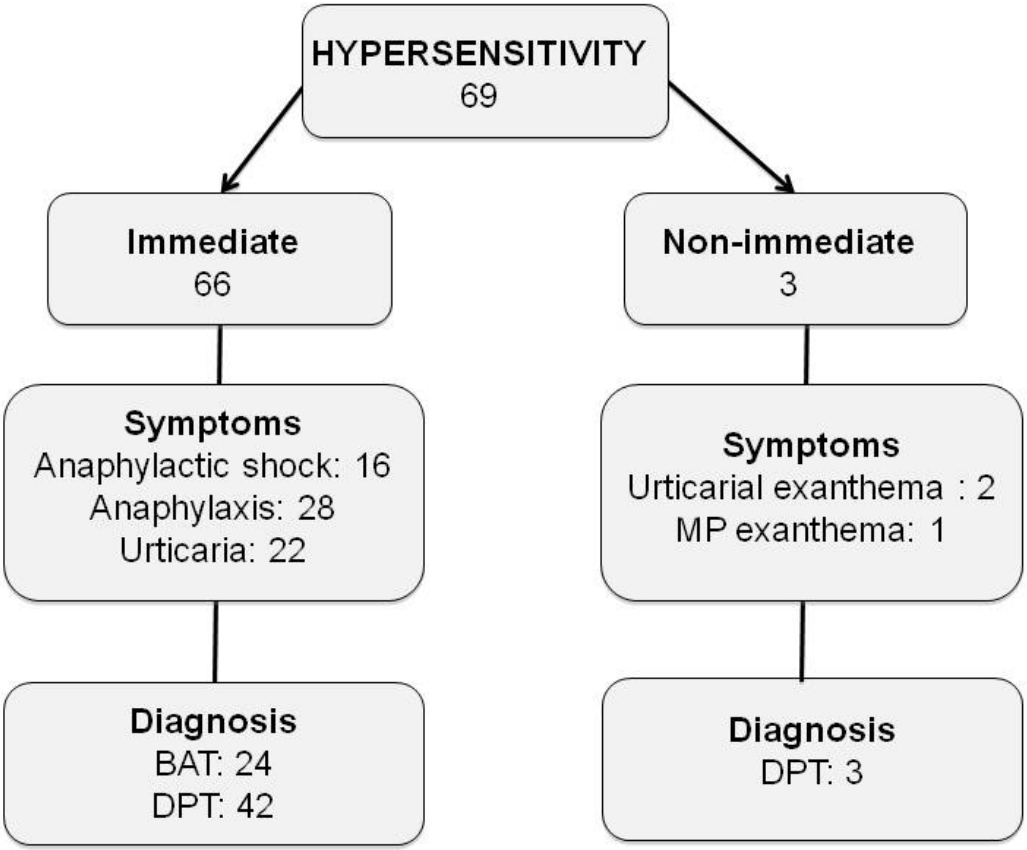
Figure 2



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Figure 3



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