ORIGINAL ARTICLE

Allergy to Quinolones: Low Cross-reactivity to Levofloxacin

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Abstract

Background: Immediate-type hypersensitivity reactions to quinolones are rare. Some reports describe the presence of cross-reactivity among different members of the group, although no predictive pattern has been established. No previous studies confirm or rule out cross-reactivity between levofloxacin and other quinolones. Therefore, a joint study was designed between 2 allergy departments to assess cross-reactivity between levofloxacin and other quinolones.
Material and Methods: We studied 12 patients who had experienced an immediate-type reaction (4 anaphylaxis and 8 urticaria/angioedema) after oral administration of quinolones. The culprit drugs were as follows: ciprofloxacin (5), levofloxacin (4), levofloxacin plus moxifloxacin (1), moxifloxacin (1), and norfloxacin (1). Allergy was confirmed by skin tests and controlled oral challenge tests with different quinolones. The basophil activation test (BAT) was applied in 6 patients.
Results: The skin tests were positive in 5 patients with levofloxacin (2), moxifloxacin (2), and ofloxacin (2). BAT was negative in all patients (6/6). Most of the ciprofloxacin-reactive patients (4/5) tolerated levofloxacin. Similarly, 3 of 4 levofloxacin-reactive patients tolerated ciprofloxacin. Patients who reacted to moxifloxacin and norfloxacin tolerated ciprofloxacin and levofloxacin.
Conclusions: Our results suggest that skin testing and BAT do not help to identify the culprit drug or predict cross-reactivity. Oral challenge testing is the only way to confirm tolerance to a quinolone before prescribing it as a safe alternative. Levofloxacin could be a safer alternative in cases of reaction to first-, second-, or fourth-generation quinolones.

Key words: Quinolone allergy. Levofloxacin. Ciprofloxacin. Drug allergy. Cross reactivity. Basophil activation test.

Resumen

Antecedentes: Las reacciones de hipersensibilidad a quinolonas son raras. Algunas publicaciones describen la presencia de reactividad cruzada entre los diferentes componentes del grupo sin un patrón repetitivo. No hay estudios en los que se descarte o confirme la presencia de reactividad cruzada entre levofloxacino y otras quinolonas. Por dicho motivo, nos planteamos el presente estudio conjunto entre dos servicios de alergología.
Material y métodos: Doce casos de reacciones alérgicas (4 de anafilaxia y 8 de urticaria / angioedema) con las siguientes quinolonas: 5 ciprofloxaino, 4 levofloxacino, 1 levofloxacino más moxifloxacino, 1 moxifloxacino y 1 norfloxacino. Se realizan pruebas cutáneas y pruebas de exposición controlada frente a diversas quinolonas a todos los pacientes, y TAB a 6 pacientes.
Resultados: Las pruebas cutáneas fueron positivas en 5 casos: levofloxacino (2), moxifloxacino (2) y ofloxacino (2). El TAB fue negativo en todos los pacientes (6/6). En la mayoría de los pacientes (4/5) alérgicos a ciprofloxacino se confirmó buena tolerancia a levofloxacino. De forma similar (3/4) los pacientes reactivos a levofloxacino toleraron ciprofloxacino. Asimismo, en los 2 pacientes alérgicos a moxifloxacino y a norfloxacino, se confirmó tolerancia con levofloxacino y ciprofloxacino.
Conclusiones: La realización de pruebas cutáneas y del TAB no resultan útiles para diagnóstico de alergia a quinolonas ni para un estudio de reactividad cruzada. La confirmación de tolerancia de una quinolona como alternativa precisa la realización de pruebas de exposición controlada. Levofloxacino puede constituir una alternativa más segura, en aquellos casos de reacción alérgica a quinolonas de primera, segunda o cuarta generación.

Palabras clave: Alergia a quinolonas. Levofloxacino. Ciprofloxacino. Alergia a medicamentos. Reactividad cruzada. Test de Activación de Basófilos.

Introduction

Immediate hypersensitivity reactions to quinolones are rare, ranging in frequency from 0.4% to 2% [1]. However, some authors report cross-reactivity among different members of the group, although they were unable to establish a repetitive pattern. One of the first publications in this area [2] described cross-reactivity between first- and second-generation quinolones, and its conclusions have been confirmed in subsequent studies, namely, that although there is considerable cross-reactivity among quinolones, no predictive pattern has been established. Sensitization to one quinolone does not predict sensitization to another member of the group. Furthermore, as skin tests provide little information, it is necessary to carry out challenge tests to confirm sensitivity or tolerability [3].

Based on their chemical structure and antibacterial activity, quinolones can be classified in 4 groups by generation: first-generation, including pipemidic acid; second-generation, including ciprofloxacin, norfloxacin, and ofloxacin; third-generation, including levofloxacin; and fourth-generation, including moxifloxacin.

Levofloxacin is the levogyre form of ofloxacin. It is an L-enantiomer in which spatial changes with total molecular similarity confer clearly differentiated pharmacodynamic characteristics; hence its inclusion in the third generation. No previous studies confirm or rule out cross-reactivity with other quinolones.

A study was designed between the Allergy Departments of Hospital Santiago Apostol in Vitoria-Gasteiz, Spain and Hospital San Pedro in Logroño, Spain to assess reactivity between levofloxacin and other quinolones in an attempt to find a safe alternative for patients who are allergic to this agent. We analyzed 12 quinolone-allergic patients who underwent a protocol to determine cross-reactivity between levofloxacin and other members of the quinolone group.

Material and Methods

The study sample comprised 12 patients (7 women and 5 men, age range 19-83 years) who had experienced an immediate-type reaction after oral administration of quinolones. Six patients were referred to the Allergy Department of Hospital Santiago Apóstol and 6 to Hospital San Pedro for diagnosis. The immediate-type reactions were anaphylaxis in 4 cases and urticaria/angioedema in 8 cases. The culprit drugs were as follows: ciprofloxacin (5 cases), levofloxacin (4 cases), levofloxacin plus moxifloxacin (1 case), moxifloxacin (1 case), and norfloxacin (1 case). The clinical features of the reactions and the drugs involved are summarized in Table 1.

Skin Tests

All patients underwent prick testing with ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. When

Table 1. Clinical Features

Patient	Age, y	Sex	Symptoms	Culprit Drug
1	61	Female	Anaphylaxis	Levofloxacin
2	43	Female	Anaphylaxis	Ciprofloxacin
3	44	Male	Anaphylaxis	Levofloxacin
4	83	Male	Urticaria	Levofloxacin
5	50	Female	Urticaria	Moxifloxacin
6	63	Female	Anaphylaxis	Norfloxacin
7	83	Male	Urticaria/angioedema	Moxifloxacin, levofloxacin
8	54	Male	Angioedema	Ciprofloxacin
9	30	Female	Urticaria/angioedema	Ciprofloxacin
10	60	Female	Angioedema	Ciprofloxacin
11	52	Female	Angioedema	Ciprofloxacin
12	19	Male	Urticaria	Levofloxacin

Table 2. Skin Test. Drug Concentrations Administered

Quinolone	Prick Test	Intradermal Test
Ciprofloxacin	0.02 mg/mL	0.02 mg/mL
Levofloxacin	5 mg/mL	0.05 mg/mL
Moxifloxacin	Tablet, 400 mg suspended in saline solution	Not tested
Norfloxacin	Tablet, 400 mg suspended in saline solution	Not tested
Ofloxacin	Tablet, 400 mg suspended in saline solution	Not tested

the results were negative, intradermal tests were performed with ciprofloxacin and levofloxacin. The results were read after 15 minutes. The skin tests performed and drug concentrations used are shown in Table 2. All skin tests were performed as described elsewhere [4].

Basophil Activation Test

All patients were studied between 3 weeks and 6 months after the reaction. One hundred microliters of heparinized whole blood was aliquoted per test. Commercial formulations of intravenous ciprofloxacin (Ciprofloxacino Normon) and levofloxacin (Tavanic) [5] were obtained from Laboratorios Normon SA (Madrid, Spain) and Sanofi Aventis (Madrid, Spain) and oral moxifloxacin (Actira) was obtained from Bayer (Barcelona, Spain). Before use, antibiotics were diluted in stimulation buffer, and 20 µL of 2 final concentrations of antibiotic was added. Ciprofloxacin was administered at final concentrations of 50 and 100 µg/mL, levofloxacin at 50 and 100 µg/mL, and moxifloxacin at 125 and 250 µg/mL. These concentrations were based on higher feasible concentrations with the commercial formulations of quinolones after being tested on 12 healthy controls to verify the lack of nonspecific activation. Twenty microliters of stimulation buffer was added as a negative control and 20 µL of stimulation buffer with fMLP or anti-IgE antibody (Sigma-Aldrich, St. Louis, Missouri, USA) was used as a positive control.

The samples were incubated at 37ºC for 15 minutes in a water bath. After cooling on ice for 5 minutes, basophils were triple-labelled by adding 20 µL of conjugated PE-anti-CD123, PerCP-anti-HLA-DR, and FITC-anti-CD-63 (FastImmune, BD Biosciences, San Jose, California, USA) to each tube. After 20 minutes of incubation at 4ºC, red blood cells were lysed (FACS lysing solution, BD Biosciences) for 10 minutes at room temperature. After centrifugation, 2 mL of washing solution was added and a new centrifugation was performed. After centrifugation, 200 µL of washing solution was added to the cell pellets and cytofluorometric analysis of $CD63^+$ cells on at least 200 $CD123^+DR^-$ cells was performed (FACScan, BD, Immunocytometry Systems). Results were considered positive when the stimulation index (SI) (ratio of $CD63^+$ cells with stimulus to the negative control) was greater than 2 and the percentage of these cells was greater than 5% in at least 1 of the dilutions with antibiotics.

Controlled Oral Challenge Test

Patients gave their written informed consent to participate. A single-blind oral challenge test with 1 or more quinolones was performed in all patients (ciprofloxacin in 9, levofloxacin in 8, and moxifloxacin in 8). We administered progressively greater doses until the therapeutic dose was reached for each agent. The doses were administered at 30-minute intervals and the patient remained under observation for 45 minutes after the last dose. The doses were administered as follows: ciprofloxacin at 50 mg, 125 mg, 250 mg, and 1 tablet (500 mg); levofloxacin at 50 mg, 125 mg, 250 mg, and 1 tablet (500 mg); and moxifloxacin at 40 mg, 100 mg, 200 mg, and 1 tablet (400 mg). Blood pressure and heart rate were measured before and after each dose.

Challenge testing was performed on different days, with a 1-week washout period between tests. Administration was stopped when a patient presented symptoms.

Results

The results of the skin and challenge tests are shown in Table 3.

The results of the flow cytometric basophil activation test (BAT) were negative in all the patients in whom it was carried out.

The skin tests were positive in 5 patients: 2 with levofloxacin (4 and 12), 2 with moxifloxacin (2 and 6), and 2 with ofloxacin (1 and 6).

Four out of 5 ciprofloxacin-reactive patients (patients 2, 8, 9, 10, and 11) tolerated levofloxacin, and only 1 case reacted to the second dose of levofloxacin (cumulative dose 175 mg):

Table 3. Results of Skin Tests and Oral Challenge Tests

Patient	Culprit	Ciprofloxacin		Levofloxacin		Moxifloxacin		Norfloxacin		Ofloxacin	
		ST	OCT	ST	OCT	ST	OCT	ST	OCT	ST	OCT
1	Lx	–	WT	–	NT	–	+	–	NT	+	NT
2	Cx	–	NT	–	WT	+	+	–	NT	–	NT
3	Lx	–	WT	–	+	–	NT	–	NT	–	NT
4	Lx	–	+	+	NT	–	+	–	NT	–	NT
5	Mx	–	WT	–	WT	–	+	–	NT	–	NT
6	Nx	–	WT	–	WT	+	+	–	NT	+	NT
7	Mx/Lx	–	WT	–	NT	–	NT	–	NT	–	NT
8	Cx	–	+	–	WT	–	WT	–	NT	–	NT
9	Cx	–	NT	–	+	–	WT	–	NT	–	NT
10	Cx	–	+	–	WT	–	WT	–	NT	–	NT
11	Cx	–	NT	–	WT	–	NT	–	NT	–	NT
12	Lx	–	WT	+	NT	–	NT	–	NT	–	NT

Abbreviation: Cx, ciprofloxacin; Lx, levofloxacin; Mx, moxifloxacin; NT, not tested; Nx, norfloxacin; OCT, oral challenge test; OCT+, not tolerated; ST, skin test; WT, well tolerated.

60 minutes after the first dose the patient developed periorbital edema, which improved with oral antihistamine. Since the skin test results were negative for ciprofloxacin in patients 8 and 10, a challenge with the culprit drug was performed in order to confirm an allergic reaction. Patient 8 had a positive reaction to the second dose (cumulative dose 175 mg) 60 minutes after the first dose, and patient 10 had a positive reaction to the third dose (cumulative dose 425 mg) 90 minutes after the first dose. In both cases, the reaction was periorbital edema accompanied by conjunctival hyperemia. The reaction improved with oral dexchlorpheniramine and, in patient 10, with intravenous methylprednisolone due to the persistence of angioedema. In patient 2, the challenge test with moxifloxacin was positive at the first dose (40 mg). The patient experienced urticaria, which improved with epinephrine.

Three out of 4 levofloxacin-reactive patients (1, 3, 4, and 12) tolerated ciprofloxacin. Patients 1 and 3 had a positive challenge test result to moxifloxacin and levofloxacin, respectively. Patient 1 experienced palmar and pharyngeal itching with persistent cough and nervousness immediately after taking 100 mg of moxifloxacin (second dose). The condition improved quickly with epinephrine.The skin test results for patient 3 were negative: 30 minutes after 125 mg of levofloxacin (second dose), the patient experienced palmar, inguinal, and pharyngeal itching with cough. The patient's condition improved quickly with epinephrine. In both cases, the clinical presentation was the same as in the initial reaction. In patient 12, no further challenge tests to other quinolones were performed, because the patient had a positive skin test result to levofloxacin.

Patients 5 (moxifloxacin-reactive) and 6 (norfloxacin-reactive) tolerated the oral challenge tests with ciprofloxacin and levofloxacin well. In both cases, the result of the challenge test with moxifloxacin was positive. Of note, although moxifloxacin was the culprit drug for patient 5, he had a negative moxifloxacin skin test result. The reaction appeared after 1 hour (400 mg) and the presentation was similar to that of the original reaction, namely, wheals and generalized itching that improved rapidly with oral dexchlorpheniramine maleate. In patient 6, the reaction appeared 1 hour after a dose of 400 mg of moxifloxacin was reached. The reaction consisted of generalized itching and erythema and dizziness, all of which were observed during the original reaction. The patient improved quickly with epinephrine, oral dexchlorpheniramine, and intravenous methylprednisolone, although the erythema persisted for the next few hours. In both cases, the initial reaction to the drug (moxifloxacin in case 5, norfloxacin in case 6) appeared 1 to 2 hours after administration.

Patient 7 presented 2 reactions with 2 different quinolones (levofloxacin and moxifloxacin), although oral ciprofloxacin was well tolerated.

No delayed reactions were observed in the challenge tests or skin tests.

Discussion

Some studies conclude that the level of cross-reactivity between quinolones is high and that if a patient is allergic to one agent of the group, then all quinolones should be avoided. Although cross-reactivity between different quinolones has been observed, the fact that some patients tolerate these agents means that it is not possible to establish a predictive pattern. Previous studies were performed with first- and second-generation quinolones [2,6-10], usually ciprofloxacin. One group reported a case of allergy to moxifloxacin in which ciprofloxacin and norfloxacin were well tolerated [11]. We previously confirmed cross-reactivity between moxifloxacin, a fourth-generation quinolone, and ciprofloxacin and ofloxacin [4]. It seems that there is no way of predicting cross-reactivity. Different patterns of cross-reactivity could be present in immediate-type reactions, as Schmid et al [12] suggested for delayed hypersensitivity reactions, when they postulated the possibility of 3 reactivity patterns through different T-cell clones.

Cross-reactivity seems to be related to the molecular ring common to all quinolones. These agents are synthetic antibiotics provided by a 4-oxo-1,4-dihydroquinoleine ring core. The basic structure of the quinolones differs from that of their predecessor, nalidixic acid, with the addition of 1 or more fluorine atoms to position 6. The differences between the other groups of fluoroquinolones are related to changes at positions 1, 5, 7, and 8 that can affect activity as well as the onset of adverse reactions. These differences are the basis for classifying the quinolones as first-, second-, third-, and fourth-generation. There are no previous reports on cross-reactivity between levofloxacin and other quinolones.

We chose ciprofloxacin and moxifloxacin to test cross-reactivity to levofloxacin based on the results of other studies [2,4,6-10]. Our results suggest that levofloxacin

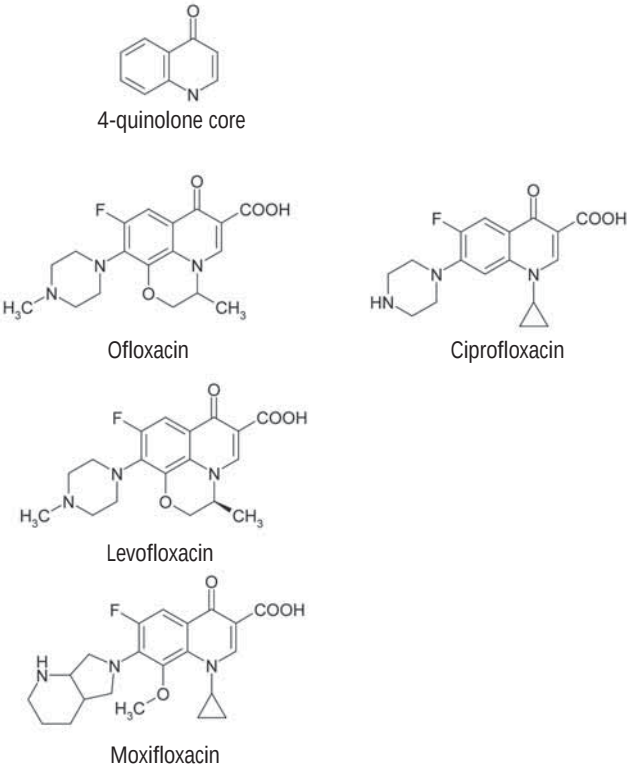

Figure. Chemical structure of levofloxacin and the quinolones.

could prove to be a valid alternative in quinolone-allergic patients. In our study, 4 out of 5 patients who reacted to ciprofloxacin showed good tolerance to levofloxacin. Similarly, in the 2 patients who reacted to norfloxacin and moxifloxacin, levofloxacin was well tolerated. Levofloxacin is the levogyre form of ofloxacin (Figure). It is an L-enantiomer in which spatial change with a similar structure confers pharmacodynamic characteristics that lead to the drug being included in the third generation. This may explain the good tolerability to levofloxacin in patients who react to the other quinolones.

Three out of 4 levofloxacin-allergic cases showed good tolerance to ciprofloxacin. In patients with primary sensitization to levofloxacin, the molecular sensitizer part could be different from that of the other quinolones.

Our data show that skin test results did not help to predict the results of the oral challenge test, since negative skin test results with positive oral challenge results have been demonstrated. Taking into account the 2 cases with cross-reactivity between levofloxacin and ciprofloxacin (cases 4 and 9), it is advisable to perform an oral challenge test before considering a quinolone as a safe alternative. Challenge tests are the safest way to confirm good tolerance to a drug [3,13,14].

The flowcytometric BAT is a new diagnostic test that could improve final diagnosis in patients who experience allergic reactions to drugs [15,16]. BAT was carried out in 6 out of 12 patients and the results were negative in all of them. Therefore, BAT did not have a positive predictive value with our patients. Furthermore, a true allergic reaction was confirmed in 5 out of the 6 cases studied (1, 2, 3, 5, and 6) by means of an oral challenge test. In a recent study, Seitz et al [14] performed BAT in 4 patients with symptoms of anaphylaxis after an oral challenge with fluoroquinolones and observed no basophil activation after administration of different fluoroquinolones. The results we present are preliminary; however, to confirm the hypothesis that BAT is not helpful in diagnosis of allergy to quinolones, further studies are necessary to assess variables such as type of quinolone, type of reaction, and onset.

We found that neither skin testing nor flowcytometric BAT was helpful in predicting cross-reactivity to quinolones or in establishing a diagnosis. Skin tests to several quinolones should be performed in order to orient the diagnostic study before exposing the patient to oral administration. Oral challenge testing can confirm tolerance before prescribing a quinolone as a safer alternative. Thus, levofloxacin could be the safer alternative in cases of reaction to first-, second- or fourth-generation quinolones. It is necessary to confirm low cross-reactivity to other quinolones, such as ofloxacin, and carry out new studies to assess whether the route of sensitization to levofloxacin could be different to that of the other quinolones.

References

1. Andriole, VT. The future of the quinolones. Drugs. 1999;58 Suppl 2:1-5.
2. Dávila I, Díez ML, Quirce S, Fraj J, De la Hoz B, Lázaro M. Cross-reactivity between quinolones. Report of three cases. Allergy. 1993;48(5):388-90.
3. Venturini Díaz M, Lobera Labairu T, del Pozo Gil MD, Blasco Sarramián A, González Mahave I. In vivo diagnostic tests in adverse reactions to quinolones. J Invest Allergol Clin Immunol. 2007;17(6):393-8.
4. González Mahave I, Lobera Labairu T, Blasco Sarramián A, del Pozo Gil MD. Hypersensitivity to fluorquinolones. J Invest Allergol Clin Immunol. 2005;15(2):146-9.
5. Ebo DG, Sainte-Laudy J, Bridts CH, Mertens CH, Hagendorens MM, Schuerwegh AJ, DeClerk LS, Stevens WJ. Flow-assisted allergy diagnosis: current applications and future perspectives. Allergy. 2006;61:1028-1039.
6. Fiandor Román AM. Otras reacciones cruzadas. Rev Esp Alergol Inmunol Clin. 1990;5(Suppl 2):95-100.
7. Arias Irigoyen J, Abengozar Muela R, García Lázaro MA, Senent Sánchez CJ. Reacción adversa por quinolonas. Estudio de reactividad cruzada. Rev Esp Alergol Inmunol Clin. 1995;10(2):87-90.
8. Alonso MD, Martín JA, Quirce S, Dávila I, Lezaun A, Sánchez Cano M. Fixed eruption caused by ciprofloxacin with cross-sensitivity to norfloxacin. Allergy. 1993;48:296-7.
9. Lozano Ayllón M, Gomez Martinez M, Mosquera MR, Laguna Martinez JJ, Orta Martiartu M, Fernandez de Miguel C. Fixed eruption caused by ciprofloxacin without cross sensitivity to norfloxacin. Allergy. 1995 Jul;50(7):598-9.
10. López San Martín M, Elices Apellániz A, Ausin Olivera A. Fixed drug eruption induced by ciprofloxacin: cross-sensitivity among quinolones. Allergy. 1998 June;53(43):99.
11. Alemán AM, Quirce S, Cuesta J, Novalbos A, Sastre J. Anaphylactoid Reaction Caused by Moxifloxacin. J Invest Allergol Clin Immunol. 2002;12(1):67-8.
12. Schmid DA, Depat JPH, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. Clin Exp Allergy. 2006;36:59-69.
13. Messaad D, Sahla H, Benhamed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004;140(12):130-7.
14. Seitz CS, Bröcker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. Clin Exp Allergy. 2009;39:1738-45.
15. Sanz ML, Maselli JO, Gamboa PM, Oehling A, Diéguez I, de Weck AL. Flow cytometric basophil activation test: a review. J Invest Allergol Clin Immunol. 2002;12(3):143-54.
16. Gamboa PM, Sanz ML, Urrutia I, Jáuregui I, Antépara I, Diéguez I, De Weck AI. CD63 expression by flow cytometry in the in vitro diagnosis of allergy to omeprazole. Allergy. 2003;58(6):538-9.

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