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THE ROLE OF IN VIVO TESTS IN THE DIAGNOSIS OF HYPERSENSITIVITY REACTIONS DUE TO QUINOLONES AND THEIR IMPORTANCE IN CROSS-REACTIONS

Hale Ates[1], Kurtuluş Aksu[1], Dilek Çuhadar Erçelebi[1]
Süleyman Türkyılmaz[1], Buket Basa Akdogan[1], Özlem Özdedeoğlu[1]
Gözde Köycü Buhari[1], İlkay Koca Kalkan[1]
[1]Ankara Atatürk Sanatoryum Training and Research Hospital, Department of Immunology and Allergy, Ankara, Turkey

Correspondence:
Hale Ates (e-mail: dr.haleates@hotmail.com)

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Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

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Abstract

Objectives: There are conflicting results regarding the sensitivity of skin tests and cross-reactions between quinolones in quinolone allergy. In our study, we aimed to evaluate the results of skin tests and provocation tests performed with quinolones and to investigate the value of these tests in the diagnosis of hypersensitivity reactions due to quinolones and their usefulness in detecting possible cross-reactions between quinolones.

Materials and Methods: We analyzed the file records of the patients who applied to our clinic for the reason of antibiotic drug allergy and who underwent diagnostic or alternative in vivo diagnostic tests with quinolone group drugs between January 2006 and September 2020. We recorded and evaluated the results of these cases with demographic characteristics such as age, gender, atopy history, concomitant allergic diseases, suspected antibiotic(s), allergic reaction type and time of occurrence, skin tests for diagnosis, and drug provocation tests.

Results: The study included 715 patients, 73.56% of whom were women. Of the patients, 92.72% had a history of early-type drug allergic reactions. Skin tests had been applied to 219 patients. Of the 119 skin tests performed for diagnostic purposes, 48 were positive. A provocation test was performed in 31 of these patients whose skin test was found to be sensitive; 27 of them were negative. In 47 patients, 83 safe cross-over alternative drugs were obtained through provocation tests.

Conclusion: Provocation tests are necessary for the diagnosis of quinolone hypersensitivity reaction and in the evaluation of cross-reactivity. Before provocation tests, evaluation should be made with skin tests.

Keywords: Antibiotics, cross-reactions, hypersensitivity reactions, quinolones.

Introduction

Quinolone group antibiotics are drugs that are effective against gram-negative and positive bacteria. Although generally considered well tolerated, they can cause allergic reactions.[1,2] Quinolones are the second most common class of antibiotics associated with drug-induced allergic reactions. However, the true prevalence of quinolone allergy in the general population is unknown.[3]

Early type (in the first 1-6 hours) or late type hypersensitivity reactions can be seen with quinolones. Immunoglobulin E (IgE) – mediated early reactions (such as urticaria, angioedema, and anaphylaxis) are most common. In cases with a history of hypersensitivity to quinolones, avoiding this drug group is the safest and simplest method.[4] However, if quinolone use is necessary, various tests have been developed to diagnose quinolone allergy. These tests are skin tests (prick, intradermal, patch tests), in vitro (radioimmunoassay (RIA) and the basophil activation test (BAT)) and drug provocation tests. Skin tests and in vitro tests exhibit low sensitivity and specificity. Drug provocation tests, on the other hand, are the preferred gold standard method to confirm quinolone allergy.[5-7]

Evidence for cross-reactivity among quinolones is limited and conflicting. There are no specific rules for predicting cross-reactivity due to quinolones, but studies and case reports have generally reported a high degree of cross-reactivity between first-generation and second-generation agents. In addition, a low degree of cross-reactivity has been reported with third-generation quinolones such as levofloxacin and newer quinolones such as moxifloxacin.[2,4]

Are skin tests less sensitive when the drug is confirmed by provocation tests? In a patient describing a hypersensitivity reaction with a quinolone, can we give another quinolone, or should we restrict the whole group? Additional work is needed to answer these questions.

In this study, we aimed to evaluate the in vivo diagnostic tests (skin tests and provocation tests) and their results performed with quinolones in our clinic and to investigate the value of these tests in the diagnosis of hypersensitivity reactions due to quinolones and their usefulness in detecting possible cross-reactions between quinolones.

Materials and Methods

Study Design and Patient Recruitment

This study was retrospectively planned in Ankara Atatürk Sanatoryum Training and Research Hospital, Allergy and Immunology Department. The study was conducted according to the declaration of Helsinki and

Participants over the age of 18 who applied to our clinic due to antibiotic drug allergy between 2006 and 2020 and who had diagnostic or alternative in vivo diagnostic tests with quinolone group drugs were included in the study.

In the study, 835 patient files were examined. A total of 120 patients were excluded from the study, including 40 patients whose history is unclear / not compatible with drug allergy, 11 patients were tested under antihistamine/corticosteroid/omalizumab treatment, and seven patients did not have a history of antibiotics and drug allergy, were tested for anxiety, and 62 patients whose file information could not be accessed.

Demographic characteristics such as age, gender, atopy history, concomitant allergic diseases, suspected antibiotic(s), allergic reaction type and time of occurrence, diagnostic skin tests and drug provocation tests were recorded from the electronic files of the patients.

The evaluation of drug allergy

In drug allergies, if a true allergy is suspected after taking a detailed patient history, classification should be made according to the duration of the reaction and the type of immune mechanism leading to the findings. Urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea) or anaphylaxis that occur 1 to 6 hours after the first dose of medication are considered early-type (Type 1) drug reactions. Maculopapular eruption (MPE), fixed drug eruption (FDE), toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), etc. that occur after 6 hours are considered as late-type (Type 2, Type 3 and Type 4) drug reactions.[8,9] Afterwards, necessary tests are performed in order to confirm the diagnosis or to obtain alternative medicine. With the information we obtained from the medical records, we classified the type of allergic reaction that occurred with the drug as early-type/late type and recorded in this way.

Skin tests

While performing the skin prick test (SPT), histamine (10 mg/mL) was used as a positive control, and physiological saline was used as a negative control. The prick test was performed with the undiluted form of the drug. If SPT was negative, an intradermal test (IDT) was performed with increasing doses at 20-minute intervals, starting with 1/1000 dilution of the drug and until reaching the maximum non-irritant concentration. The test was considered positive if the diameter of edema in the test area was found to be more than 3 mm compared to the negative control. If the IDT 20th minute readings were negative for delayed reactions, the late readings were evaluated at 24, 48, 72 hours and seven days after the administration of the tests. In the patch

tests performed on the same day as the IDT, drug allergens and control material (the carrier material with which the drug is mixed (example: Vaseline)) were adhered to the patient's skin with a hypoallergenic tape in non-irritant concentrations within the chambers. The test material was removed 48 hours after the test was applied, and the test area was marked and evaluated after 15-20 minutes. Patch test readings were taken on 48th, 72nd (and ±96th hours) and seventh day.

If all skin tests were negative and there were no contraindications, a drug provocation test (DPT) was continued. In our study, SPT, IDT and patch test results of the patients with drugs were found by examining their file records and recorded as negative/positive.

Drug provocation tests

DPT was performed by the oral way in a placebo-controlled, single-blind fashion. The test was started with drug doses ranging from 1/1000 to 1/10 depending on the severity of the reaction in the history. Drug doses were administered at 30-minute intervals until a positive result was obtained or until the daily treatment dose was reached.

If any signs of hypersensitivity related to the skin, respiratory system, cardiovascular system, gastrointestinal system or neurological system occurred during the SPT or during the waiting period predicted according to the history after the test, the test result was considered positive and terminated. In this case, the necessary medical treatment was applied to the patient, and the patient was kept under observation until all findings were resolved. The test was considered negative in patients who could use the last dose of the drug without any problems and did not develop any symptoms during the waiting period. With the information obtained from the patient records, the DPTs performed on the patients were recorded for diagnostic/alternative purposes, and the results were recorded as negative/positive. All drug tests were performed under hospital conditions and in an environment where emergency response conditions were met. Written informed consent was obtained from patients for skin and challenge testing.

Statistical analysis

Predictive analytical software (PASW statistics 18, 2009) was used for the analysis. A type-I error level of less than 5% was used to infer statistical significance. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean and standard deviation for numerical variables. For categorical variables, in two–group comparisons, the Chi-square test was used when the chi-square condition was met, and the Fisher Test simulation was used when the chi-square condition was not met.

Results

The mean age of 715 patients included in the study was 46±13 years, and 526 were female. The most common accompanying allergic diseases were asthma, chronic urticaria and allergic rhinitis, respectively. Sensitivity to at least one allergen was detected in 83 patients whose allergen sensitivity was investigated by a skin prick test and specific immunoglobulin E (spIgE) (Table 1).

It was determined that the history of allergic reactions due to antibiotics developed primarily due to beta-lactams and secondly to quinolones. Ciprofloxacin in 57 cases, moxifloxacin in 23 cases, and levofloxacin in 15 cases were the most frequently reported quinolone antibiotics. Of the patients, 663 had a history of early-type allergic reactions, and 52 had late-type allergic reactions. The most common early-type drug reactions were anaphylaxis, urticaria and angioedema, respectively, and late-type drug reactions were FIE and MPE (Table 2).

Table 1. Demographic Characteristics of Study Population

Variables	**N: 715**
Age, (year)	46±13
Gender, n(%)	
Female	526 (73.56)
Male	189 (26.43)
Concomitant allergic diseases, n(%)	
Asthma	150 (20.97)
Chronic urticaria	56 (7.83)
Allergic rhinitis	45 (6.29)
Venom allergy	10 (1.39)
Food allergy	7 (0.97)
Atopic dermatitis	6 (0.83)
Atopy, n(%)	
Pollen	47 (6.57)
House dust mite	32 (4.47)
Mold	10 (1.39)
Venom	12 (1.67)
Food	7 (0.97)

Diagnostic drug testing was performed in 220 (30.76%), alternative drug testing was performed in 444 (62.10%) patients, and cross-alternative drug testing was performed in 51 (7.13%) patients.

A total of 656 (91.75%) patients underwent DPT, and 219 (30.63%) skin tests (SPT and/or IDT) were performed. Skin tests were diagnostic in 119 patients, 43 with the responsible drug and 76 with the suspected drug. Among the diagnostic skin tests, SPT was positive in 2 patients, and IDTs were positive in 46 patients. In

these patients, whose sensitivity was determined by skin test measurement, the test was negative in 27 of 31 DPTs performed with the responsible/suspicious drug.

In 47 patients with a history of quinolone antibiotics, DPT tests performed with other quinolone antibiotics were negative. And safe cross-alternative medicine is provided. A total of 83 safe cross-over drugs were obtained with DPTs in 47 patients, 29 patients with a history of ciprofloxacin, nine patients with a history of moxifloxacin, three patients with a history of levofloxacin, five patients with a history of Gemifloxacin, and one patient with a history of ofloxacin (Figure 1a – e). Positivity was detected in the DPTs of 12 patients, which were performed for the purpose of finding alternatives. A significantly higher rate of DPT positivity was observed in women. It was observed that the rate of positivity in SPTs was not associated with concomitant allergic disease, sensitivity to at least one allergen, or the presence of multiple drug allergies.

Table 2. Suspected drugs causing the reaction and observed clinical findings

Variables	**n = 715**
Suspect drug causing drug reaction, n(%)	
Beta Lactam	553 (77.34)
Quinolone	102 (14.26)
Macrolide	86 (12.02)
Azole	30 (4.19)
Sulfonamide	21 (2.93)
Tetracycline	12 (1.67)
Aminoglycoside	2 (0.27)
Unknown	185 (25.87)
Clinical findings observed with drug intake, n(%)	
Urticaria	179 (25.03)
Angioedema	114 (15.94)
Itching	90 (12.58)
Erythema	79 (11.04)
Gastrointestinal symptoms	23 (3.21)
Bronchospasm	19 (2.65)
Laryngeal edema	8 (1.11)
Rhinitis	5 (0.69)
Anaphylaxis	274 (38.32)
Fix drug eruption	29 (4.05)
Maculopapular eruption	19 (2.65)
Stevens-Johnson Syndrome	1 (0.13)
Toxic epidermal necrolysis	1 (0.13)
Drug reaction with eosinophilia and systemic symptoms	1 (0.13)
Vasculitis	1 (0.13)

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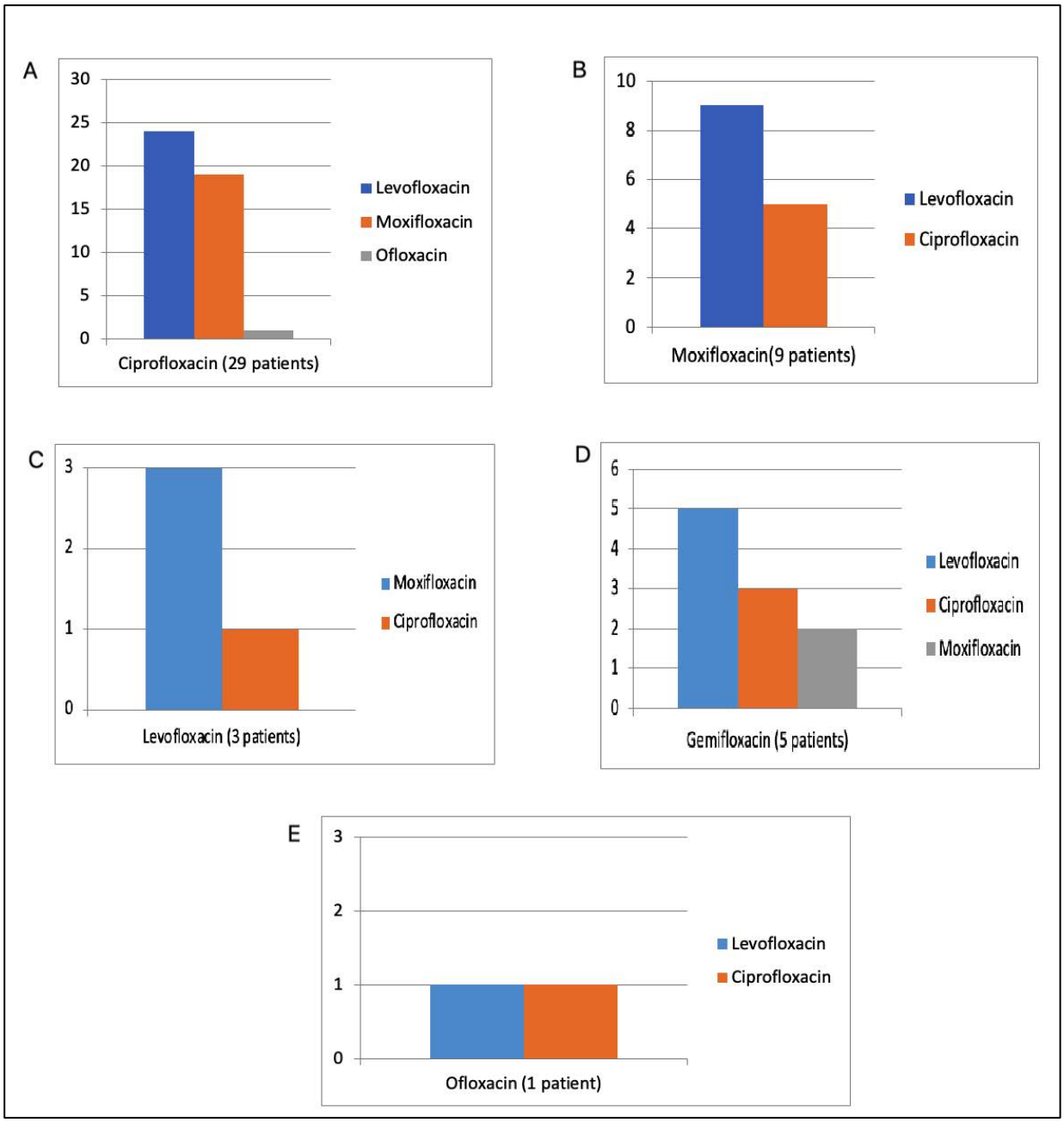

Figure 1. Identification of safe alternatives among quinolones

(A: Negative results on drug provocation tests with levofloxacin, moxifloxacin and ofloxacin in 29 patients describing an allergic reaction to ciprofloxacin. **B:** Negative results on drug provocation tests with levofloxacin and ciprofloxacin in 9 patients describing an allergic reaction to moxifloxacin. **C:** Negative results on drug provocation tests with moxifloxacin and ciprofloxacin in 3 patients describing an allergic reaction to levofloxacin. **D:** Negative results on drug provocation tests with levofloxacin, ciprofloxacin and moxifloxacin in 5 patients describing an allergic reaction to Gemifloxacin. **E:** Negative results on drug provocation tests with levofloxacin and ciprofloxacin in 1 patient describing an allergic reaction to ofloxacin.)

Discussion

In our study, drug reactions were evaluated in 715 patients who presented with a history of early or late antibiotic allergy. As observed in a multicenter study conducted in our country in 2013 evaluating the perception of drug allergy, beta-lactam group antibiotics were found to be the most frequently reported suspicious drugs in our study.[10] Consistent with the literature in our study, quinolone group antibiotics were followed with the second frequency. Although quinolones are generally known to be well-tolerated antibiotics, in recent decades, there has been an increase in quinolone allergy.[2,3,11,12]

Our main aim in our study was to answer the questions of how many of the antibiotic drug reactions evaluated in our clinic were able to perform diagnostic skin tests and provocation tests and whether we could provide safe quinolones as a result of these tests. However, it is a fact that accurate diagnosis of quinolone allergy is not easy due to low sensitivity in skin tests, high probability of false positives and unknown pathogenic mechanisms.[4,13,14] In a study conducted by Eva Perez et al. in which 48 patients were evaluated, it was observed that SPTs had low sensitivity, and IDTs had a high rate of false positive results (88%) due to the irritant and histamine-stimulating effect of the drug. And for this reason, skin tests are considered to be of limited utility for diagnosing quinolone hypersensitivity.[14] In a study conducted by Venturini Díaz et al., in which 71 patients were evaluated by skin tests, ten patients with a positive skin test were given a drug provocation test, and five were positive. A drug provocation test was applied to 34 patients whose skin test was negative, and 32 of them were negative. The skin test results were thought to help predict the provocation test result.[5]

In our study, SPT was found to be positive in 2 patients, and IDTs were positive in 46 patients from the diagnostic skin tests performed on 119 patients. In these patients, whose sensitivity was determined by skin test measurement, the test was negative in 27 of 31 SPTs performed with the responsible/suspicious drug. In a retrospective study by Seitz et al., in which they examined the results of diagnostic tests in quinolone allergy, 89 out of 101 patients had negative skin tests, and when DPT was continued in these patients, quinolone allergy was excluded with a negative result in 71 patients.[15] As can be understood from this, diagnosing drug allergy based on anamnesis often leads to an unnecessary diagnosis of drug allergy. If a true drug allergy is suspected in the patient describing drug allergy after careful evaluation of the medical history, skin tests should be planned according to the clinical findings described first. Patients with a negative skin test should be evaluated with a provocation test. In a study by Demir et al. in which 54 patients with a history of hypersensitivity reactions to quinolones were evaluated, it was observed that the contribution of skin tests to the diagnosis and cross-sensitization was low. For this reason, the necessity of performing a provocation test to identify the culprit or alternative drug was emphasized.[16]

The most frequently accused quinolones in our study were ciprofloxacin, moxifloxacin and levofloxacin, respectively. Although the order of quinolones varies between studies, the most frequently accused quinolones in the literature are ciprofloxacin, moxifloxacin and levofloxacin, respectively, similar to our study.[5,15,17] In another study, the accused drugs were followed as moxifloxacin, ciprofloxacin and levofloxacin, respectively.[7] It is thought that the ranking in this study may be related to their higher consumption in clinical practice compared to others.[3]

Cross-reactions between quinolones are still controversial due to conflicting results among publications. In some publications consisting of case reports and series, a high degree of cross-reactivity has been reported, especially between first-generation agents (nalidixic acid) and second-generation agents (norfloxacin, ciprofloxacin).[6,18] A lower degree of cross-reactivity has been reported in some publications, particularly with third-generation quinolones such as levofloxacin and newer quinolones such as moxifloxacin.[17,19] For the detection of alternative quinolones in this drug group with cross-reaction potential, skin tests can be performed, taking into account the previous reaction type and severity and provocation tests if negative. In our study, as a result of the provocation tests we conducted, we were able to obtain 83 safe alternative quinolones in 47 patients.

One of the limitations of our study is that we could not perform in vitro tests such as specific IgE determination and BAT. Our study is a retrospective study, and these tests are expensive and not applied in clinical routine. Another limitation of ours is that we could not perform a diagnostic test with the responsible drug in more patients. It could be evaluated by an oral provocation test considering the false-positive rate in quinolones with a positive skin test.

As a result, unnecessary diagnosis of drug allergy can be avoided by performing skin tests for quinolone group drugs and provocation tests, if negative, in accordance with the patient's history. In cases where diagnostic tests are hesitant, cross-reactivity can be ruled out by skin tests and if negative, by provocation tests, alternative quinolones can be provided.

Ethical Considerations: Ethical approval was acquired from the Keçiören Training and Research Hospital (Ethics Committee No: 10.11.2020/ 2186).

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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