ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Cutaneous hypersensitivity to quinolones and associated factors

Determinação da reatividade cutânea às quinolonas e fatores associados

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ABSTRACT

Introduction: Quinolones, widely used in clinical practice, are the second leading cause of antibiotic hypersensitivity. Hypersensitivity to quinolone poses a challenge for allergists, as it occurs through immunoglobulin E (IgE)-mediated mechanisms as well as nonimmunologic ones (specifically the MRGPRX2 receptor). **Objective:** To assess cutaneous hypersensitivity to ciprofloxacin at different concentrations. **Methodology:** Skin prick test (SPT) and immediate-reading intradermal test (IDT) with ciprofloxacin were performed on volunteers treated at a tertiary outpatient clinic. Concentrations of 2 mg/mL (main solution), 1:10, and 1:50 were used for the SPT, and concentrations of 1:10, 1:50, 1:100, and 1:500 were used for the IDT. **Results:** Thirty-one individuals with no history of hypersensitivity to quinolone were included, of whom 74.1% were women. Mean patient age was 40.5 years. Atopic diseases were found in 48.4% of participants, of whom 100% had allergic rhinitis, 20% had allergic conjunctivitis, 13.3% had asthma, and 13.3% had atopic dermatitis. Previous quinolone use was reported by 45.2%. SPT performed with the main solution and 1:10 dilution was positive in 25.8% and 6.5% of cases, respectively, whereas SPT with 1:50 dilution was negative in all cases. IDT performed with 1:10, 1:50, and 1:100 dilutions was positive in 96.8%, 45.2%, and 6.5% of cases, respectively, but negative with 1:500. Among the individuals who had used quinolones, SPT with main solution and 1:50 dilution was positive in 28.6% and 14.3% of cases, respectively, compared with 25% and 0% in those who had not used quinolones. Among those who had used quinolones, IDT results were positive in 100% at 1:10, 57.1% at 1:50, and 14.3% at 1:100. Among those who had not used quinolones, IDT results were positive in 93.7% at 1:10, 37.6% at 1:50, and 0% at 1:100. In atopic individuals, SPT was positive in 26.7% with the main solution and 1:10 dilution, and negative with 1:50. Among nonatopic individuals, 25% had a positive SPT with the main

RESUMO

Introdução: As quinolonas, amplamente usadas na prática clínica, correspondem à segunda causa de reações de hipersensibilidade aos antibióticos. Reações às quinolonas (RQ) são um desafio para o alergista, pois ocorrem por mecanismos IgE mediados, mas também por uma via não imunológica, o receptor MRGPRX2. **Objetivo:** Este trabalho avalia a reatividade cutânea de pessoas sem alergia ao ciprofloxacino em diversas concentrações. **Metodologia:** Foram realizados *prick tests* (PT) e testes intradérmicos de leitura imediata (ID) com ciprofloxacino em voluntários atendidos em um ambulatório de serviço terciário. No PT, foram usadas concentrações de 2 mg/mL (solução mãe), 1:10 e 1:50. No ID, 1:10, 1:50, 1:100 e 1:500. **Resultados:** Foram incluídos 31 indivíduos sem histórico de RQ. A média de idade foi de 40,5 anos, sendo 74,1% do gênero feminino. Doenças atópicas foram encontradas em 48,4% dos participantes, 100% destes com rinite alérgica, 20% com conjuntivite alérgica, 13,3% com asma, e 13,3% com dermatite atópica. Uso prévio de quinolonas foi relatado por 45,2% dos indivíduos. O PT puro e 1:10 foi positivo em 25,8% e 6,5%, respectivamente; na concentração 1:50 não mostrou positividade. O ID 1:10, 1:50 e 1:100 foi positivo em 96,8%, 45,2% e 6,5%, respectivamente, mas foi negativo na diluição 1:500. Nos que já usaram quinolonas, o PT puro e 1:50 foram positivos em 28,6% e 14,3% dos participantes, respectivamente, *versus* 25% e 0% nos que não usaram. O ID entre os indivíduos que já usaram foi positivo em 100% na diluição 1:10, 57,1% na 1:50, e 14,3% na 1:100. Entre os que não usaram, 93,7% na diluição 1:10, 37,6% na 1:50, e 0% na 1:100. Nos atópicos, o PT foi positivo em 26,7% e 13,3% na concentração mãe e 1:10; e negativo em 1:50. Nos participantes não atópicos, observou-se positividade de 25% no PT com a solução mãe e testes negativos nas demais diluições. O ID com as soluções 1:10, 1:50 e 1:100 foi positivo em 100%, 46,7% e 6,7% dos atópicos, e 93,7%,

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solution, and the remaining individuals were negative. IDT results with 1:10, 1:50, and 1:100 dilutions were positive, respectively, in 100%, 46.7%, and 6.7% of atopic individuals and in 93.7%, 43.7%, and 6.3% of nonatopic individuals. **Conclusion:** Ciprofloxacin triggers cutaneous hypersensitivity via immunologic mechanisms and the MRGPRX2 receptor. It is recommended that skin tests be performed at a dilution of 1:100 or greater to investigate immediate hypersensitivity.

Keywords: Quinolone allergy, skin tests, skin prick test, intradermal tests, ciprofloxacin.

43,7%, 6,3% nos não atópicos, respectivamente. **Conclusão:** O ciprofloxacino apresenta reatividade cutânea através de vias imunológicas e pelo MRGPRX2, sendo recomendada a realização de testes cutâneos em concentrações igual ou menores de 0,02 mg/mL para investigação de reações de hipersensibilidade imediata, pois essas concentrações apresentam boa especificidade.

Descritores: Alergia a quinolonas, testes cutâneos, teste de puntura, testes intradérmicos, ciprofloxacino.

Introduction

Quinolones are broad-spectrum antibacterial drugs that were first obtained during the synthesis of chloroquine and then chemically evolved throughout the years, leading to the development of nalidixic acid, which acts predominantly on gram-negative bacteria causing urinary tract infection, and modern antibiotics that enter into several sites, have a broad spectrum activity, and are used in the treatment of more resistant microorganisms.[1]

The basic chemical structure of quinolones consists of a 4-oxo-1,4- dihydroquinoleine ring core with a hydrogen atom at position 1 and a carboxyl acid at positions 3 and 4. Since the synthesis of the first quinolones, several chemical changes have been made, improving their efficacy, spectrum of action, bacterial activity, and tissue penetration. Quinolones have been classified into four generations, based on their chemical structure and antibacterial spectra. The chemical structure of quinolones and their classification are presented in Figure 1.[2]

The first-generation quinolones – nalidixic acid, pipemidic acid, cinoxacin, oxolinic acid – are active against gram-negative bacteria, and their penetration is restricted to the urinary tract. The second generation, developed with the introduction of the fluorine atom at position C-6, includes fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, fleroxacin, lomefloxacin, enoxacin) and has broad-spectrum activity against gram-negative bacteria g gram-positive bacteria. The addition of a halogen (fluorine or chlorine) at position 8 leads to third-generation quinolones – levofloxacin and gatifloxacin –, which have greater activity against *Pseudomonas aeruginosa*, gram-positive bacteria, and anaerobes. Finally, the fourth generation – moxifloxacin, gemifloxacin, and trovafloxacin – is more potent against gram-positive bacteria and anaerobes and less active against *P. aeruginosa*, due to a double ring derived from the pyrrolidone ring at position 7 and a methoxy group at position 8.[3,4]

Bactericidal activity of quinolones targets the bacterial enzymes DNA gyrase and DNA topoisomerase IV, inhibiting microorganism replication.[1,4,5] Currently, these antibiotics are widely used in the treatment of gram-positive and gram-negative bacteria affecting the urinary, respiratory, digestive, and cutaneous tracts, in addition to sexually transmitted infections, prostatitis, and tuberculosis.[5]

Due to the widespread use of quinolones, adverse events related to the use of these drugs have been described. Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as “any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function”. These reactions can be classified into type A – predictable and dose-dependent; and type B – unpredictable, dose-independent, and not directly associated with the effects of the drug.[6]

Drug hypersensitivity reactions (DHRs) are defined by the WHO as type B ADRs resembling allergy and reproducible in subsequent administrations. The term drug allergy should be used when there is a specific immunological mechanism associated with clinical manifestations, involving either drug-specific immunoglobulins or T cells.[6]

DHRs to quinolones are the second leading cause of hypersensitivity to antibiotics and the third leading cause of hypersensitivity to medications in general, after non-steroidal anti-inflammatory drugs

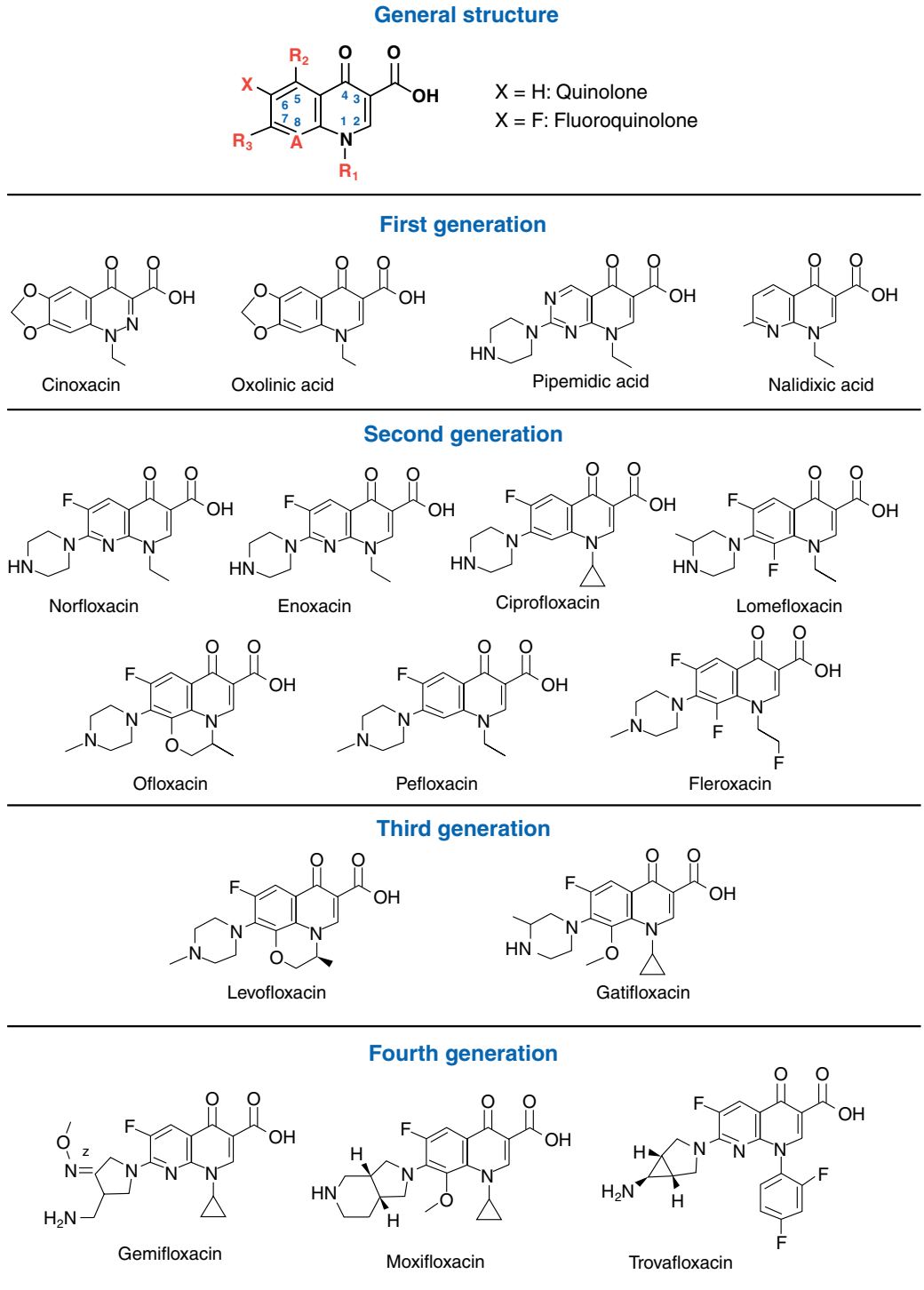

Figure 1
Chemical structure and classification of quinolones
Adapted from Doña I, et al.[2].

and beta-lactams in frequency.[7] These reactions are classified into immediate, which usually involve urticaria and other symptoms associated with anaphylaxis, or delayed T cell-mediated reactions, such as maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), or acute generalized exanthematous pustulosis.[2,8]

Immediate DHRs to quinolones, resulting from the activation of mastocytes and basophils, may occur through different endotypes, despite having the same phenotype. The presence of quinolone-specific IgE was identified in 30 to 55% of individuals with history of immediate DHRs[8-10]; however, in some individuals, these medications may trigger reactions via other mechanisms, such as agonist action at MRGPRX2 (mast-related G-protein receptor X2), present in mast cells, basophils, and eosinophils, leading to the activation of these cells.[2,11]

In clinical practice, the diagnosis of immediate DHRs to quinolones is based on detailed clinical history of the symptoms and previous use of the medication involved, which is correlated with the reaction throughout time. Additional tests, such as skin tests and provocation tests, are important investigation tools. *In vitro* tests, such as specific IgE tests and basophil activation tests may be used, despite being little available and having greater application in research.[2,12,13]

Investigation with skin tests starts with the skin prick test, or skin puncture, test. In case of a negative result, investigation continues with the immediate-reading intradermal test. Despite being widely used in clinical practice for DHRs to other drug classes, the use of skin tests for quinolones is controversial, since these drugs may generate positive results via two mechanisms – presence of specific IgE and agonistic action at MRGPRX2, depending on the concentration used.[2,14]

Determining the drug dilution concentration to be used in skin tests in essential. More concentrated solutions may induce "irritant" skin reactions in individuals with no history of DHR, or, in the case of quinolones, via MRGPRX2 present in skin mast cells. Therefore, the predictive positive value of skin tests should be interpreted in light of possible interferences.

In addition to the concentrations used to perform the skin tests, other conditions may influence the results, such as skin reactivity, presence of comorbidities, and use of antihistamines and antidepressants. Hence, knowledge of skin reactivity at different concentrations used in skin tests with quinolones, associated with analysis of possible interfering factors, may help in better understanding mast cell homeostasis, in addition to potentially predicting the most appropriate dilution to be used in the diagnostic investigation of immediate DHRs to quinolones.

This work had the primary objective of assessing reactivity of skin, epicutaneous (prick) and immediate-reading intradermal tests to quinolones in a population with no history of hypersensitivity to these medications. The study made it possible to determine the concentration of ciprofloxacin that has good specificity in skin tests to investigate immediate reactions to the antibiotic. As a secondary objective, the study analyzed possible factors associated with skin reactivity to ciprofloxacin in immediate-reading skin tests.

Methods

This work consisted of a cross-sectional analytical assessment of the study population, composed of individuals with no history of immediate hypersensitivity reaction to quinolones. Adult volunteers older than 18 years of age treated at the outpatient clinics of the Clinical Immunology and Allergy Service of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Individuals with history of hypersensitivity to quinolones were excluded, as well as those receiving antihistamine treatment in the last 7 days prior to the skin test and those who had anaphylaxis at any point in life, mast cell activation syndrome, cutaneous or systemic mastocytosis, spontaneous or induced chronic urticaria, and extensive skin disease that prevented the execution of skin tests.

Initially, an interview was conducted for collection of medical history - age, sex, previous use of quinolones, presence of atopic diseases, and personal or family history of hypersensitivity to other medications. Next, a prick test was performed to assess sensitization to aeroallergens with extract of *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, cat and dog epithelium, *Lolium perenne*, *Aspergillus sp*, *Penicillium notatum*, *Blatella germanica*, and *Periplaneta americana.*

Finally, skin reactivity to ciprofloxacin was evaluated. The puncture test was conducted with the following concentrations: 2 mg/mL (pure solution),

0.2 mg/mL (1:10), and 0.04 mg/mL (1:50). The immediate-reading intradermal test was performed with the following concentrations: 0.2 mg/mL (1:10), 0.04 mg/mL (1:50), 0.02 mg/mL (1:100), and 0.0004 mg/mL (1:500). The prick test was considered positive if the allergen produced a wheal 3 mm larger than the negative control (saline solution), whereas the intradermal test was considered positive if the difference between the initial and final size of the wheal was 3 mm larger than the difference observed in the negative control. Skin tests were performed in duplicate on the anterior surface of both forearms.

Statistical analysis was performed using the Python platform, with data from Excel® files. The data collected included patients' characteristics and test results, which were converted for binary values. All continuous variables were expressed as means and their respective standard deviations. An initial descriptive analysis was performed, followed by application of the Student's *t* test for paired samples. Categorical variables were presented as absolute numbers and percentages, and compared using the chi-square test (χ^2). P-values lower than 0.05 were considered significant. Bar graphs were created using Matplotlib and Seaborn.

Results

This study included 31 individuals with no history of hypersensitivity to quinolones. Mean age was 40.5 years (standard deviation 13.0 years), and 74.1% of individuals were female. Atopic diseases were reported in 48.4% of participants – among these, 100% reported allergic rhinitis, 20% allergic conjunctivitis, 13.3% asthma, and 13.3% atopic dermatitis. Of total participants, 45.2% reported previous use of quinolones; of these, 32.2% had contact with ciprofloxacin, 32.2% with levofloxacin, and 0.03% with moxifloxacin. These data are described in Table 1. Age distribution is shown in Figure 2.

In the total population, the prick test with pure ciprofloxacin and 1:10 dilution was positive in 25.8% and 6.5% of the sample, respectively, whereas no positive results were found with the 1:50 dilution. The intradermal test at the 1:10, 1:50 and 1:100 dilutions was positive in 96.8%, 45.2%, and 6.5% of the sample, respectively. There were no positive results with the 1:500 dilution. Therefore, specificity was 93.5% for both the prick test with the 1:10 dilution and the intradermal test with 1:100 dilution.

The prick test for aeroallergens was positive in 54.9% of the evaluated individuals. Among these, puncture with ciprofloxacin was positive in 23.5% and 11.8% for pure ciprofloxacin and 1:10 dilution, respectively. The intradermal test with the antibiotic was positive in 100%, 52.9%, and 5.8% for 1:10, 1:50, and 1:100 dilutions, respectively. Therefore, 1:100 dilution showed good specificity (94.2%) in individuals with atopy.

Patients with a negative result for aeroallergens accounted for 45.1% of the cases, of which 28.6% were positive in the prick test with pure ciprofloxacin, but negative with the other dilutions. The intradermal test with ciprofloxacin was positive in 99.9%, 35.8%, and 7.2% with 1:10, 1:50, 1:100 dilutions, respectively.

No statistical differences were observed in the results of the chi-square tests for each type and dilution of the skin test with ciprofloxacin comparing individuals with positive and negative results in the test for aeroallergens.

In the subgroup of volunteers with atopic diseases, the puncture test was positive in 26.7% and 13.3% with pure ciprofloxacin and 1:10 dilution, respectively. The intradermal test with 1:10, 1:50, and 1:100 dilutions was positive in 100%, 46.7%, and 6.7%, respectively.

Table 1
Demographic and clinical data of the population

	N: 31
Mean age	40.5 years
Female gender	74.1%
Atopic diseases	48.4%
Allergic rhinitis	100%
Allergic conjunctivitis	20%
Asthma	13.3%
Atopic dermatitis	13.3%
Previous use of quinolones	45.2%
Ciprofloxacin	32.2%
Levofloxacin	32.2%
Moxifloxacin	0.03%

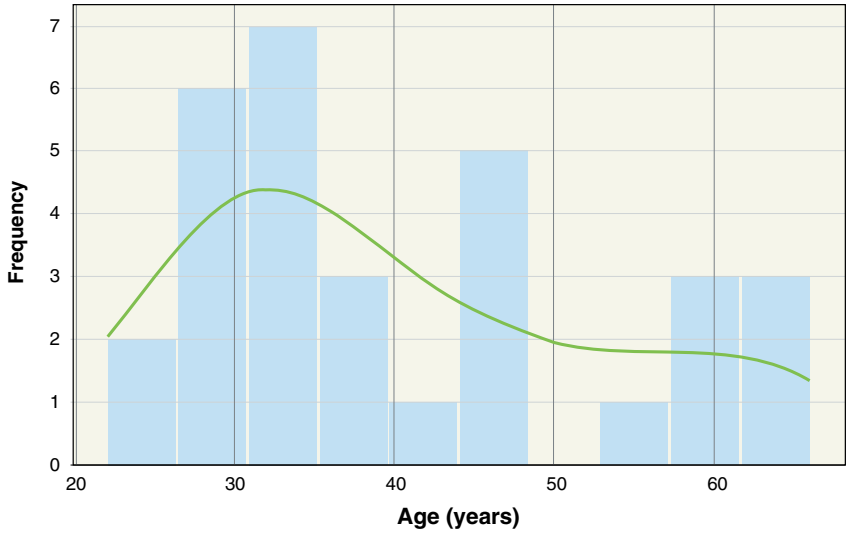

Figure 2
Age distribution in the analyzed population

Among participants without atopic diseases, 25% had a positive prick test with pure ciprofloxacin, and negative with the other dilutions. The intradermal test with 1:10, 1:50 and 1:100 dilutions was positive in 93.7%, 43.7%, and 6.3% of the nonatopic participants.

No statistical differences were observed in the assessment of the chi-square tests for skin tests with ciprofloxacin and for presence or absence of atopic diseases.

In the population that reported previous use of quinolones, the prick test with pure ciprofloxacin and 1:10 dilution was positive in 28.6% and 14.3% of the cases, respectively, vs 25% and 0% in those who did not use quinolones. The intradermal test at 1:10, 1:50, and 1:100 dilutions was positive 100%, 57.1%, and 14.3%, respectively, among those who used the antibiotic. Among those who did not use it, the intradermal test with 1:10, 1:50, and 1:100 dilutions was positive in 93.7%, 37.6%, and 0% of the cases, respectively.

Results for the chi-square tests comparing previous use of quinolones revealed a $p = 0.3$ for prick test with pure ciprofloxacin and 1:10 dilution, and $p = 0.9$, $p = 0.4$, and $p = 0.2$ for intradermal tests at 1:10, 1:50, and 1:100 dilutions, respectively.

Among all the volunteers, 74.2% denied previous ADRs to any medication; of these, 26.0% and 43% had a positive prick test with pure ciprofloxacin and 1:10 dilution, respectively, and 95.6%, 52.1%, and 4.3% showed positive skin reactivity in the intradermal test with 1:10, 1:50, and 1:100 dilutions, respectively.

The participants who reported a type A or B ADR accounted for 25.8% of the cases, of which 25.0% and 12.5% showed positive skin reactivity in the prick test with pure ciprofloxacin and 1:10 dilution, respectively. When these participants were assessed using the intradermal test with 1:10, 1:50, and 1:100 dilutions, there was reactivity in 100%, 25%, and 12.5% of the cases, respectively.

The chi-square tests did not reveal statistically significant differences between the skin test of participants with and without previous ADR.

Table 2 shows positivity rates in the general study population and according to associated factors: positive epicutaneous test for aeroallergens, presence of atopic disease, previous use of quinolones, and history of drug reactions. Tables 3, 4, 5 and 6 compare positivity rates of intradermal tests according to four associated factors: sex, positive epicutaneous test for aeroallergens, presence of atopic disease, and previous use of quinolones.

Table 2
Positivity of skin tests in the subgroups evaluated

General population - N = 31	Prick test, pure ciprofloxacin: 25.8% Prick test, 1:10 dilution: 6.5% ID test, 1:10 dilution: 96.8% ID test, 1:50 dilution: 45.2% ID test, 1:100 dilution: 6.5%
Positive prick test for aeroallergens - N = 17	Prick test, pure ciprofloxacin: 23.5% Prick test, 1:10 dilution: 11.8% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 52.9% ID test, 1:100 dilution: 5.8%
Atopic diseases - N = 15	Prick test, pure ciprofloxacin: 26.7% Prick test, 1:10 dilution: 13.3% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 46.7% ID test, 1:100 dilution: 6.7%
Previous use of quinolones - N = 15	Prick test, pure ciprofloxacin: 28.6% Prick test, 1:10 dilution: 14.3% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 47.1% ID test, 1:100 dilution: 14.3%
Other ADR - N = 8	Prick test, pure ciprofloxacin: 25.0% Prick test, 1:10 dilution: 12.5% ID test, 1:10 dilution: 100% ID test, 1:100 dilution: 25% ID test, 1:100 dilution: 12.5%

ADR = adverse drug reaction, ID = intradermal.

Discussion

Drug hypersensitivity reactions (DHRs), either allergic or not, are underdiagnosed in some scenarios, but may also be overly attributed to patients, leading to misdiagnoses of allergy in healthy individuals. This situation may hamper future therapeutic approaches, in which less effective and more expensive medications are used as alternatives.[6,15]

The execution of skin tests for betalactam antibiotics is already well established, as well as algorithms to define what portion of the molecule is more likely to be involved in sensitization. For quinolones, applicability

Table 3
Positivity of intradermal tests according to participants' sex

	Intradermal test dilutions		
Sex	**1:10**	**1:50**	**1:100**
Female	100%	45.8%	0.8%
Male	85.7%	42.8%	0

of these tests seems to be more controversial, since their concentrations are not well established, and they may lead to positive results through immunological and non-immunological (irritative) pathways.

Table 4
Positivity of intradermal tests according to positivity of epicutaneous tests for aeroallergens

Epicutaneous test for aeroallergens	Intradermal test dilutions		
	1:10	1:50	1:100
Positive	100%	52.9%	5.8%
Negative	99.9%	35.8%	7.2%

Table 5
Positivity of intradermal tests according to the presence of atopic disease or not

Atopic disease	Intradermal test dilutions		
	1:10	1:50	1:100
Present	100%	46.7%	6.7%
Absent	93.7%	43.7%	6.3%

Table 6
Positivity of intradermal tests according to previous use of antibiotic

Previous use of quinolones	Intradermal test dilutions		
	1:10	1:50	1:100
Yes	100%	57.1%	14.3%
No	93.7%	37.6%	0

HRs to quinolones, which represent broad spectrum antibiotics used in several clinical conditions, are difficult to investigate. In this work, a considerable number of individuals with no history of ADRs to these medications showed skin reactivity to different concentrations of ciprofloxacin. This result reflects the practical difficulty in performing an investigation of HRs to these medications.

Broz et al. assessed skin reactivity with ciprofloxacin through intradermal skin tests with the 1:300, 1:1000, and 1:3000 concentrations in 15 volunteers with no history of HR to quinolones. Readings in these tests were made using photograph records and analysis of wheal growth via a computational software, in addition to application of laser Doppler fluoroscopy to evaluate changes in skin perfusion. For the concentration of 1:300, no wheal growth was observed, despite the increase in blood flow; hence, this concentration was considered to be nonirritant.[16]

Venturini Díaz et al. used ciprofloxacin at a concentration of 0.02 mg/mL (1:100) for puncture and intradermal tests, levofloxacin at 5 mg/mL for the prick test and at 0.05 mg/mL for the intradermal test, and other oral quinolones (norfloxacin, ofloxacin, moxifloxacin, pipemidic acid, trovafloxacin) administered in tablets diluted in saline solution for the prick test, in 12 individuals without HR to quinolones. Of these participants, 3 had a positive prick test for ofloxacin, 1 for moxifloxacin, and 1 for pipemidic acid.[17]

In our work, both the prick test with 1:10 dilution and the intradermal test with 1:100 dilution had a specificity of 93.5%, being the most recommended concentrations for skin tests to rule out hypersensitivity to quinolones. Previous use of these drugs and ADR to other medications led to higher positivity rates at a concentration of 1:100, which may suggest previous sensitization, although the difference was not statistically significant. Atopy or presence of atopic diseases did not interfere with the results of the skin tests.

In the medical literature, there is no current consensus on the use of skin tests in the approach of HRs to quinolones, and there are authors in favor and against the use of these tests, with the latter recommending to perform only the provocation test, a procedure that carries some risks.[15,18]

Due to these limitations, skin tests are not conducted very often in individuals with a history of hypersensitivity, leading to a scarcity of data on

sensitivity in individuals subjected to the provocation test, opening the possibility for future studies.

Conclusion

In our work, the prick test with 1:10 dilution and the intradermal test with 1:100 dilution had a specificity of 93.5%, being these the concentrations recommended for skin tests to rule out hypersensitivity to quinolones. Individuals who previously used these drugs or had an ADR to other medications tended to show greater reactivity at lower concentrations; however, additional studies are needed to define sensitivity to skin tests and their clinical applicability.

References

1. Naeem A, Badshah SL, Muska M, Ahmad N, Khan K. The Current Case of Quinolones: Synthetic Approaches and Antibacterial Activity. Molecules. 2016 Mar 28;21(4):268.
2. Doña I, Blanca-López N, Boteanu C, Cueva-Oliver B, Fernández-Sánchez FJ, Gajate P, et al. Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to Quinolones. J Investig Allergol Clin Immunol. 2021 Jul 26;31(4):292-307.
3. Dalhoff A, Schmitz FJ. In vitro antibacterial activity and pharmacodynamics of new quinolones. Eur J Clin Microbiol Infect Dis. 2003 Apr;22(4):203-21.
4. Sousa J, Alves G, Fortuna A, Falcão A. Third and fourth generation fluoroquinolone antibacterials: a systematic review of safety and toxicity profiles. Curr Drug Saf. 2014;9(2):89-105.
5. Bush NG, Diez-Santos I, Abbott LR, Maxwell A. Quinolones: Mechanism, Lethality and Their Contributions to Antibiotic Resistance. Molecules. 2020 Dec 1;25(23):5662.
6. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014 Apr;69(4):420-37.
7. Doña I, Moreno E, Pérez-Sánchez N, Andreu I, Hernández Fernandez de Rojas D, Torres MJ. Update on Quinolone Allergy. Curr Allergy Asthma Rep. 2017 Aug;17(8):56.
8. Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. Curr Allergy Asthma Rep. 2005 Jan;5(1):15-21.
9. Aranda A, Mayorga C, Ariza A, Doña I, Rosado A, Blanca-Lopez N, Andreu I, Torres MJ. In vitro evaluation of IgE-mediated hypersensitivity reactions to quinolones. Allergy. 2011 Feb;66(2):247-54.
10. Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, et al. Detection of specific IgE to quinolones. J Allergy Clin Immunol. 2004 Jan;113(1):155-60.
11. Elst J, Maurer M, Sabato V, Faber MA, Bridts CH, Mertens C, Van Houdt M, et al. Novel Insights on MRGPRX2-Mediated Hypersensitivity to Neuromuscular Blocking Agents And Fluoroquinolones. Front Immunol. 2021 Jul 27;12:668962.
12. Doña I, Torres MJ, Montañez MI, Fernández TD. In Vitro Diagnostic Testing for Antibiotic Allergy. Allergy Asthma Immunol Res. 2017 Jul;9(4):288-98.
13. Giavina-Bianchi P, Gonçalves DG, Zanandréa A, Borges de Castro R, Garro LS, Kalil J, et al. Anaphylaxis to quinolones in mastocytosis: Hypothesis on the mechanism. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):2089-90.
14. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature. 2015 Mar 12;519(7542):237-41.
15. Kitsos N, Cassimos D, Xinias I, Agakidis C, Mavroudi A. Management of antibiotic allergy in children: a practical approach. Allergol Immunopathol (Madr). 2022 Sep 1;50(5):30-8.
16. Brož P, Harr T, Hecking C, Grize L, Scherer K, Jaeger KA, et al. Nonirritant intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. Allergy. 2012 May;67(5):647-52.
17. 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 Investig Allergol Clin Immunol. 2007;17(6):393-8.
18. Blanca-López N, Andreu I, Torres Jaén MJ. Hypersensitivity reactions to quinolones. Curr Opin Allergy Clin Immunol. 2011 Aug;11(4):285-91.

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