Original Article

Immediate hypersensitivity to quinolones: moxifloxacin cross-reactivity

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Abstract. *Introduction:* Immediate hypersensitivity reactions to quinolones are rare. Moxifloxacin is a new quinolone chemically different from other fluoroquinolones. We report 6 patients diagnosed with hypersensitivity to different fluoroquinolones in whom the response to moxifloxacin and cross-reactivity with other quinolones was studied.
Material-Methods: An allergenic study was made by prick and intradermal test with different fluoroquinolones, in all the patients.
Single blind oral challenge tests were performed with moxifloxacin in all the patients, with ciprofloxacin in five patients, with levofloxacin in three patients and with ofloxacin in one patient.
Results: The skin test performed with moxifloxacin was positive in five patients, and the oral challenge test was positive in all six patients.
All the patients had at least one positive skin test with some of the other fluoroquinolones.
Conclusion: The skin test with different quinolones seems to be sensitive at showing group hypersensitivity, but not at predicting specific tolerance of each drug.
We found a high degree of cross-reactivity among fluoroquinolones, so we currently recommend to avoid the group.
We did not find that moxifloxacin differed from other fluoroquinolones so we cannot recommend it as a valid therapeutic alternative in patients sensitized to other quinolones.

Key words: hypersensitivity, moxifloxacin, quinolones, skin test.

Introduction

Immediate hypersensitivity reactions to quinolones are rare, ranging in frequency from 0.4% to 2% [1], and including erythema, itching, urticaria, skin rash, and shock.

Quinolones may be classified in four groups, based on their chemical structure and their antibacterial activity. The first generation group includes pipemidic acid; the second one embraces ciprofloxacin, norfloxacin and ofloxain. In the the third generation group we find levofloxacin, and in the fourth one fluoroquinolone moxifloxacin. Figure 1 shows the chemical structure of the fluoroquinolones tested.

Moxifloxacin is a new quinolone with a methoxy group (CHO-) on carbon 8 that differentiates it chemically from other fluoroquinolones, which is why some authors suggest that it may be a valid therapeutic alternative for patients with hypersensitivity to other quinolones [2].

Skin tests with different fluoroquinolones in healthy controls have disclosed a high percentage of false positives in published studies [3]. Skin tests performed in patients under study for the administration of these medications have also yielded discrepant results [4-6], so their diagnostic value is still uncertain. The oral challenge test is still the golden standard for determining the tolerance of these medications. We report 6 patients with a diagnosis of hypersensitivity to different fluoroquinolones in whom the response to moxifloxacin and cross-reactivity with other quinolones was studied.

Material and methods

Six patients (5 women and 1 man, age range 29-63 years), presenting with an immediate reaction after the oral

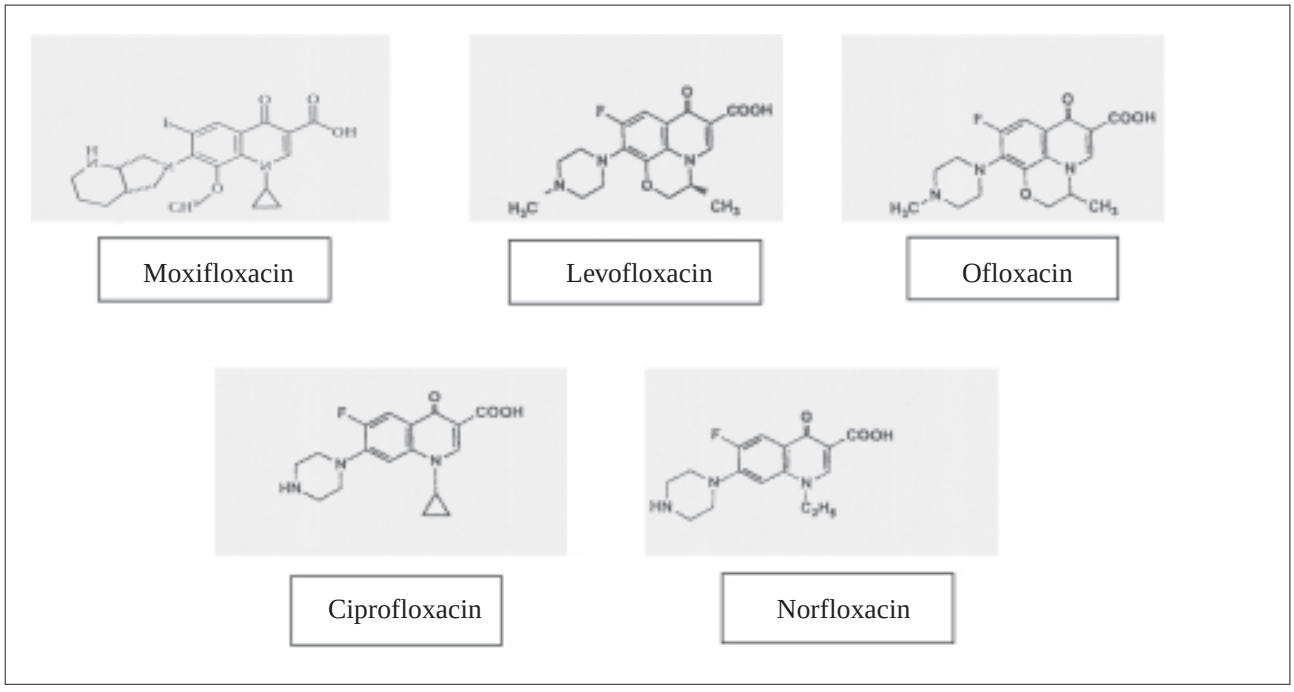

Figure 1. Chemical structure of quinolones tested.

Table 1. Clinical characteristics of the patients.

Patient	Years/Sex	Clinic	Culprit drug
1	39 Female	Urticaria	Ciprofloxacin
2	50 Female	Urticaria	Moxifloxacin
3	29 Female	Urticaria	Ofloxacin Ciprofloxacin
4	42 Female	Urticaria	Ciprofloxacin
5	63 Female	Anaphylaxia	Moxifloxacin
6	53 Male	Urticaria	Moxifloxacin

Table 2. Skin test. Drug concentrations used.

	Prick	Intradermal
Ciprofloxacin	0,02 mg/ml	0,02 mg/ml
Ofloxacin	tablet, 400 mg suspended in NaCI	
Levofloxacin	5 mg/ml	0,05 mg/ml
Norfloxacin	Tablet, 400 mg suspended in NaCI	
Moxifloxacin	Tablet, 400 mg suspended in NaCI	

administration of different quinolones, were referred to our deparment for diagnosis. The clinical characteristics of the patients and medications involved are summarized in Table 1.

Skin tests

Prick test with ciprofloxacin, ofloxacin, levofloxacin, norfloxacin, and moxifloxacin and intradermal tests with ciprofloxacin and levofloxacin were performend in all the patients. Test results were read after fiteen minutes. For intracutaneous test we used those concentrations with negative results: five nonatopic and 5 atopic patients were used as controls.

The skin tests performed and drug concentrations used are shown in Table 2.

Controlled oral challenge

Written informed consent was given by the patients. A single blind oral challenge test was performed with moxifloxacin in all patients, and challenge tests were performed with ciprofloxacin and levofloxacin in 3 patients and with ofloxacin in 1 patient. We administered progressively greater doses until reaching the therapeutic dose for each medication. The doses were given with 30 minute intervals from each other and the patient was observed 45 minutes after the last dose. We began administration of moxifloxacin from (40 mg), (100 mg), (200 mg) and 1 tablet (400 mg); ofloxacin from (20 mg),

Table 3. Results

	Culprit Drug	Ciprofloxacin		Norfloxacin		Levofloxacin		Ofloxacin		Moxifloxacin	
		Skin test	Oral challenge test	Skin test	Oral challenge test	Skin test	Oral challenge test	Skin test	Oral challenge test	Skin test	Oral challenge test
Patient 1	Ciprofloxacin	+	NT	–	NT	+	NT	–	NT	+	+
Patient 2	Moxifloxacin	+	+	–	NT	–	NT	+	+	+	+
Patient 3	Ofloxacin Ciprofloxacin	–	WT	–	NT	+	+	–	NT	+	+
Patient 4	Ciprofloxacin	–	+	–	NT	+	WT	+	NT	+	+
Patient 5	Moxifloxacin	–	WT	–	NT	–	WT	+	NT	+	+
Patient 6	Moxifloxacin	+	WT	–	NT	–	NT	–	NT	–	+

WT: Well-tolerated. NT: no test; +; positive

(50 mg), (100 mg), and 1 tablet (200 mg); levofloxacin from (50 mg), (125 mg), (250 mg) and 1 tablet (500mg) and similarly for ciprofloxacin. The blood pressure and heart rate were measured before and after each dose.

A different day was used for each medication with one-week interval between each provocation. The administration was suspended at the very moment a symptom appeared.

In those cases in which moxifloxacin was the medication responsible, patients were tested to confirm the diagnosis. In patients in whom another quinolone was involved, moxifloxacin tolerance was studied to determine its suitability as an alternative treatment.

Results

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

The moxifloxacin challenge test was immediately positive in all 6 patients with the initial dose of 40-mg.

The clinical manifestations of 4 patients were mild, consisting of itching and scattered wheals which diminished following oral treatment with antihistamines. Symptoms were more intense in the other 2 patients, with palmar and genital itching, dry cough, and dyspnea requiring epinephrine treatment to achieve remission.

In those cases with positive exposure to ciprofloxacin and/or levofloxacin, the symptoms were also elicited after a short time interval and by a low dosage.

The reactions were mild, with scattered wheals that remitted with antihistamines.

No delayed reaction was produced in any of the tests.

Discussion

The quinolones are generally well tolerated. The spectrum of adverse reactions to quinolones ranges from gastrointestinal symptoms, which are the most frequent, to neuropsychiatric symptoms, hematologic abnormalities, and, less frequently, hypersensitivity skin reactions.

Although rare (0.4-2%), hypersensitivity reactions to quinolones can occur. The clinical manifestations described include erythema, itching, urticaria, and skin rash, as well as exanthema, photodermatitis, and multisystemic reactions of an anaphylactoid type, and the presence of IgE is not evident. The incidence of these reactions is estimated to be 0.46-1.2/100,000 treatments [7]. Quinolones are synthetic antibiotics. The core of their structure is a 4-oxo-1,4-dihydroquinoleine

ring. The basic structure of fluoroquinolones differs from that of their predecessor, nalidixic acid, in the addition of 1 or more fluorine atoms to position 6. The differences between fluoroquinolones are related to changes in positions 1, 5, 7, and 8 that can affect activity as well as the onset of adverse effects. These differences are the basis for classifying the quinolones as first, second, third, and fourth generation.

Moxifloxacin presents the core fluoroquinolone nucleus and its molecular structure is halfway between ciprofloxacin and ofloxacin, but carbon 8 presents a methoxy group (CH_3O) that differentiates moxifloxacin from other fluoroquinolones.

Cross-reactivity studies between quinolones have been published. These studies conclude that the level of cross-reactivity is important and all quinolones are recommended to be avoided. [3-6]. The hypothesis is that cross-reactivity is related to the ring common to all the molecules.

With the recent introduction of moxifloxacin, other studies have evaluated the potential cross-reactivity between moxifloxacin and other quinolones [8,9]. In our study 3 patients with urticaria due to another quinolone also reacted to moxifloxacin after the oral exposure test. In contrast, in the 3 patients in which the original reaction was elicited by moxifloxacin, 2 tolerated other quinolones.

These results imply the presence of a high degree of cross-reactivity between different groups of quinolones, although it may not be complete.

As proposed by other authors, the development of clinical manifestations in our patients suggests an IgE-mediated allergic mechanism. The rapid onset of symptoms after the first contact with the drug in the exposure test and the type of clinical manifestations reported support this hypothesis.

Although the pathogenic mechanism of these reactions has not yet been established, a recently published article (10) has reported the detection of quinolone-specific IgE, concluding that immediate reactions to quinolones seem to be IgE-mediated.

Our results show that skin tests did not help to predict the result of the oral exposure test: since we observed negative skin tests with positive oral challenge and positive skin test with good tolerance in the challenge test, for every drug.

Nonetheless, all patients had at least one skin positive test, with independence of the tolerance in the oral challenge. In reference to ciprofloxacin, the quinolone tested in prick and intradermal, we observed negative results in prick in all the patients, with intradermal positive results in three of them, which suggests that former test could be more sensitive for detecting of sensitization to quinolones. Therefore, we think that it is interesting to note that skin tests were sensitive for detecting group sensitivity, but not sensitivity to a specific drug.

Consequently, we believe it is advisable to perform skin tests with several quinolones as a way of orienting the diagnostic study before exposing the patient to oral administration.

Conclusion

In our study, the positive result obtained in the skin tests with different quinolones seems to be sensitive for showing group hypersensitivity, but not for predicting specific tolerance of each drug.

We found a high degree of cross-reactivity between fluoroquinolones, so we currently recommend to avoid this group.

In contrast with other authors, we did not find that moxifloxacin differed from other fluoroquinolones, so we cannot recommend it as a valid therapeutic alternative in patients sensitized to other quinolones.

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