

Immediate Hypersensitivity to Moxifloxacin with Tolerance to Ciprofloxacin: Report of Three Cases and Review of the Literature

Brenda Chang, Sandra R Knowles, and Elizabeth Weber

Since the discovery of the quinolones in 1962, this class of antibiotics has gained much popularity in the treatment of various infectious diseases.¹ Extensive structural modifications, including the introduction of a fluorine atom, have been made to enhance the spectrum of activity and oral bioavailability of this class of antibiotics. Today, the fluoroquinolones are the only synthetic antibacterial agents that have gained worldwide clinical use comparable to that of the β -lactam antibiotics.²

Fluoroquinolone antibiotics are generally well tolerated. The most common adverse effects reported involve the gastrointestinal tract (~1–5%), the skin (<2.5%), and the central nervous system (CNS) (~1–2%).^{3–6} Immune-mediated hypersensitivity reactions have also been reported at a frequency of 1 in 50,000 treatments.⁷ Immediate immunoglobulin E (IgE)-mediated hypersensitivity reactions, such as urticaria, angioedema, and anaphylactic shock, are the most frequently described immune-mediated reactions. However, rare reports of delayed maculopapular exanthems, Stevens-Johnson syndrome and toxic epidermal necrolysis, fixed drug eruptions, hematologic disorders, acute interstitial nephritis, acute hepatitis, and cholestatic jaundice can also be found.^{7,8} Anaphylactoid reactions, which have the same presentation as anaphylactic reactions due to the release of histamine

OBJECTIVE: To report 3 cases of immediate hypersensitivity reactions to moxifloxacin in patients who tolerated ciprofloxacin.

CASE SUMMARIES: A 71-year-old man, a 44-year-old woman, and a 70-year-old woman with a history of a moxifloxacin reaction developed an immediate hypersensitivity reaction upon oral challenge with moxifloxacin in our Drug Safety Clinic. The reaction was mainly characterized by pruritus and urticaria, although dyspnea and hypotension were noted in the first and second patient, respectively. Two of the patients had negative oral challenge tests with ciprofloxacin and all 3 patients tolerated full treatment courses of oral ciprofloxacin. In all 3 cases, use of the Naranjo probability scale indicated a highly probable adverse drug reaction.

DISCUSSION: Moxifloxacin, similar to other fluoroquinolones, can cause immediate hypersensitivity reactions. Previous publications have reported both cross-reactivity and a lack of cross-reactivity among various fluoroquinolones. The 3 patients discussed demonstrated a lack of cross-reactivity between moxifloxacin and ciprofloxacin since they tolerated oral challenge tests and full treatment courses of ciprofloxacin. Moxifloxacin has unique side chains at positions 7 and 8 on its bicyclic ring structure. Antigenic specificity to particular side chains at positions 7 and 8 on the bicyclic ring structure of moxifloxacin may explain this lack of cross-reactivity. Higher reporting rates of anaphylaxis to moxifloxacin compared to other fluoroquinolones may also be related to side chain specificity, although definitive evidence for this is lacking.

CONCLUSIONS: Based on our experience, patients who develop immediate hypersensitivity reactions to moxifloxacin may receive ciprofloxacin therapy in an appropriately monitored setting if they have previously tolerated full treatment courses of ciprofloxacin. Research into whether there is a specific side chain reaction unique to moxifloxacin is warranted.

KEY WORDS: anaphylaxis; ciprofloxacin; cross reactions; fluoroquinolones; hypersensitivity, immediate; moxifloxacin.

Ann Pharmacother 2010;44:740-5.

Published Online, 16 Mar 2010, *theannals.com*, DOI 10.1345/aph.1M579

Author information provided at end of text.

from mast cells and basophils, but which are not IgE-mediated, have also been reported with the fluoroquinolones.⁸ Anaphylactoid reactions can occur with the first dose, as prior sensitization is not required. Although not immune-mediated, these reactions are considered immediate hypersensitivity reactions and are managed in the same way.

Moxifloxacin is a third-generation fluoroquinolone, with markedly improved gram-positive activity that is commonly prescribed for respiratory tract infections.³ Other advantages include a lower resistance rate compared to levofloxacin and a lower risk of adverse effects, including a lower propensity for inducing phototoxic reactions and CNS adverse effects compared to other fluoroquinolones.^{5,9} Nevertheless, unpredictable immediate hypersensitivity reactions have been reported with moxifloxacin despite its overall safety profile, with evidence suggesting that anaphylaxis is more frequently reported with moxifloxacin compared to ciprofloxacin, ofloxacin, and levofloxacin.¹⁰⁻¹²

We describe 3 patients in whom we confirmed an immediate hypersensitivity reaction to moxifloxacin with an oral challenge test, but who previously tolerated full treatment courses of ciprofloxacin. Use of the Naranjo probability scale¹³ indicated that an adverse drug reaction attributable to moxifloxacin was highly probable. In addition, the propensity for cross-reactivity and structural differences between moxifloxacin and other fluoroquinolones are reviewed in this report.

Case Reports

A 71-year-old male was referred to our Drug Safety Clinic 5 months after developing urticaria when administered moxifloxacin. At the time of his reaction, he was being treated with moxifloxacin 400 mg daily for a bronchiectasis exacerbation. He tolerated the first dose; however, 30 minutes after taking the second dose, he developed nausea, dyspnea, hot flashes, and generalized urticaria. He also vomited, but denied any swelling. He discontinued moxifloxacin after the second dose and self-medicated with diphenhydramine and cold compresses. His symptoms resolved after several hours.

This patient’s past medical history included coronary artery disease, hyperlipidemia, chronic obstructive pulmonary disease with bronchiectasis, pulmonary fibrosis, and diabetes. He had no known drug allergies prior to his reaction to moxifloxacin. At the time of his bronchiectasis exacerbation, he was taking multiple long-term medications, which included albuterol, tiotropium, salmeterol, fluticasone, glyburide, amlodipine, ezetimibe, pravastatin, and prednisone when required. In addition, he stated that he had previously tolerated ciprofloxacin, levofloxacin, and 1 course of moxifloxacin.

Intradermal skin tests to fluoroquinolones (Table 1) and an oral challenge to ciprofloxacin 250 mg were performed 5 days after the patient’s interview in the Drug Safety Clinic. He was not taking prednisone at the time and he was instructed to avoid antihistamines for 48 hours prior to completing his skin tests and oral challenge. Histamine 1 mg/mL and NaCl 0.9% were used as controls. Results of his intradermal skin tests and subsequent ciprofloxacin oral challenge were negative.

Two months later, the patient returned for an oral challenge to moxifloxacin 200 mg. On this visit, he reported that he had just completed a 2-week course of ciprofloxacin. His baseline blood pressure was 151/81 mm Hg, heart rate 102 beats/min, and peak expiratory flow 180 L/min. Within 15 minutes after the dose, the patient complained of generalized pruritus, dyspnea, and hot flashes. On examination, there was no apparent urticaria or rash and his vital signs remained stable. Forty minutes after the initial dose, he continued to complain of pruritus. His symptoms progressed to nausea, wheezing, and urticaria on his arms and back, similar to his previous experience with moxifloxacin. He was treated with 0.5 mL of subcutaneous epinephrine 1:1000, 50 mg of oral diphenhydramine, and 10 mg of oral cetirizine. Five hours later, all of his symptoms had resolved and he was discharged home.

Three months after the moxifloxacin oral challenge, the patient was contacted to determine whether he had taken further treatment courses with other fluoroquinolones. He informed us that he completed a 15-day course of ciprofloxacin without any adverse effects 1 month after his reaction to the moxifloxacin oral challenge.

Table 2 provides a summary of patient characteristics and allergy test results for the above patient and 2 additional patients who were tested for reactions to moxifloxacin over 5 years in our Drug Safety Clinic. Unlike the first patient, the 2 additional patients had not taken any previous doses of moxifloxacin prior to their initial reaction and appeared to present with anaphylactoid reactions; however, we did not confirm their history of moxifloxacin use. In addition, the second patient had previously tolerated levofloxacin and the third patient had previously tolerated ciprofloxacin prior to the skin tests and oral challenges in our clinic. Analogous to the first patient, these 2 patients developed symptoms that were similar to those of their initial reaction to moxifloxacin within 20 minutes to 2 hours of their moxifloxacin oral challenge. Subsequent to the moxifloxacin oral challenge, the third patient completed at least 5 additional courses of ciprofloxacin without any adverse effects. We were unable to contact the second patient to deter-

Table 1. Drug Concentrations Used for Intradermal Skin Tests and Oral Challenge Tests

Drug	Intradermal	Oral Challenge
Levofloxacin	0.005 mg/mL 0.05 mg/mL	
Ciprofloxacin	0.005 mg/mL 0.05 mg/mL	250 mg
Moxifloxacin	0.005 mg/mL 0.05 mg/mL	200 mg*

*Patients 2 and 3 received a 400-mg dose due to a change in our testing protocol.

Table 2. Summary of Patient Characteristics and Test Results

Pt., Age/ Sex	History	Chronic Drug Therapy at Time of FQ Tests	Allergies	Initial Reaction to Moxi 400 mg	FQ Test Results			Reaction to Moxi OC	FQ Treatment Between Cipro and Moxi OC, n	FQ Treatment After Moxi OC, n
					IDT	OC				
1, 71/M	CAD, hyperlipidemia, COPD, bronchiectasis, pulmonary fibrosis, DM	Albuterol, tiotropium, salmeterol, fluticasone, glyburide, amlodipine, ezetimibe, pravastatin	none known	30 min after 2nd dose: nausea, dyspnea, hot flashes, urticaria, vomiting	Cipro – Levo – Moxi –	Cipro – Levo ND ^a Moxi +		15 min after OC: pruritus, dyspnea, hot flashes 40 min after OC: pruritus, nausea, urticaria on arms and back, wheezing	Cipro, 1	Cipro, 1
2, 44/F	None	None	Ampicillin, delayed reaction	30 min after 1st dose: pruritus of the throat, palms, soles; weakness; lightheadedness	Cipro – Levo – Moxi ND ^b	Cipro – Levo ND ^a Moxi +		20 min after OC: urticaria, pruritus of throat, weakness, vomiting, hypotension 2 h after OC: pruritus of palms and soles	Cipro, 1	Unknown
3, 70/F	Diverticulosis, IBS	Calcium, vitamin D	TMP/SMX, measles-like eruption	60 min after 1st dose: urticaria and pruritus of the neck and scalp	Cipro ND ^c Levo ND ^c Moxi ND ^c	Cipro ND ^c Levo ND ^c Moxi +		2 h after OC: urticaria and pruritus of the neck and scalp	None	Cipro, >5

CAD = coronary artery disease; Cipro = ciprofloxacin; COPD = chronic obstructive pulmonary disease; DM = diabetes; FQ = fluoroquinolone; IBS = irritable bowel syndrome; IDT = intradermal skin test; Levo = levofloxacin; Moxi = moxifloxacin; ND = not done; OC = oral challenge; TMP/SMX = trimethoprim/sulfamethoxazole.

^aPatients 1 and 2 declined further levofloxacin oral challenge tests.

^bPatient 2 was seen prior to the introduction of moxifloxacin intradermal tests to our standard fluoroquinolone tests.

^cPatient 3 was not prescribed the standard fluoroquinolone tests in our clinic and completed only a moxifloxacin oral challenge.

mine whether she tolerated other fluoroquinolones after her moxifloxacin oral challenge; however, this patient tolerated 1 course of ciprofloxacin between her ciprofloxacin oral challenge and moxifloxacin oral challenge.

Discussion

Immediate hypersensitivity reactions such as anaphylactic or anaphylactoid reactions have been documented with various quinolones, including ciprofloxacin,¹⁴⁻³⁰ norfloxacin,³¹ ofloxacin,³² levofloxacin,³³⁻³⁵ moxifloxacin,^{10,11} and several other quinolones not available in North America.³⁶⁻⁴¹ Based on spontaneous adverse drug reaction reports, fluoroquinolone-associated anaphylaxis has been estimated to be 1.8–2.3 per 10 million days of treatment, depending on the fluoroquinolone studied.⁴¹

Alemán et al.¹⁰ were the first to report on an anaphylactoid reaction secondary to moxifloxacin. They described a 26-year-old woman who developed generalized urticaria, labial angioedema, dyspnea, dysphonia, dysphagia, and conjunctival injection 20 minutes after exposure to moxifloxacin. Results of a skin prick test using 200 mg/mL and an oral challenge test using 25 mg of moxifloxacin were negative. However, this patient developed pruritus, wheals, nausea, and conjunctival injection after a 50-mg oral challenge dose. She was subsequently given ciprofloxacin and norfloxacin oral challenge tests at therapeutic doses. She tolerated both of these fluoroquinolones without any adverse effects. The authors therefore concluded that cross-reactivity between moxifloxacin and these 2 fluoroquinolones did not exist for this patient and called for further research to refute cross-reactivity between moxifloxacin and other fluoroquinolones.

In all 3 of our patients, immediate hypersensitivity to moxifloxacin using an oral challenge test of 200 mg or 400 mg was confirmed. All 3 patients developed symptoms similar to those of their initial reaction to moxifloxacin within 15 minutes to 2 hours of the oral challenge test (Table 2). Similar to the patient in the Alemán et al.¹⁰ report, 2 of our patients reacted to an oral challenge of moxifloxacin, but not to an oral challenge of ciprofloxacin. The first and second patient also tolerated one course of ciprofloxacin treatment between the time of their ciprofloxacin oral challenge and moxifloxacin oral challenge. In addition, 2 of our patients received full treatment courses of ciprofloxacin after a positive reaction to moxifloxacin oral challenge. Thus, cross-reactivity between moxifloxacin and ciprofloxacin did not appear to exist in any of the 3 patients. Of interest, the first and second patients also tolerated at least one course of levofloxacin prior to the initial moxifloxacin reaction, but we were unable to confirm tolerance to levofloxacin because both of these patients declined an additional levofloxacin oral challenge.

In cases of immediate hypersensitivity reactions, cross-reactivity is often presumed between the inciting agent and

other fluoroquinolones. To our knowledge, only 3 publications have specifically examined cross-reactivity among the fluoroquinolones related to immediate hypersensitivity reactions.^{11,38,42} Dávila et al.³⁸ were the first of these to evaluate the existence of cross-reactivity between first-generation (nalidixic acid, pipemidic acid) and second-generation (norfloxacin, ciprofloxacin) fluoroquinolones. In the 3 patients who were studied by Dávila et al.,³⁸ only oral challenge tests were useful in establishing cross-reactivity. They did not complete any specific in vitro IgE tests. The first patient had positive oral challenge tests to nalidixic acid and norfloxacin. The second patient had positive oral challenge tests to pipemidic acid and ciprofloxacin. The third patient had positive oral challenge tests to pipemidic acid and nalidixic acid, but interestingly, not to norfloxacin. Therefore, cross-reactivity could be demonstrated between the first- and second-generation fluoroquinolones, but not in all cases. Subsequent to this report, Manfredi et al.⁴² examined the usefulness of using in vitro testing involving quinolone-specific IgE to determine cross-reactivity. IgE to specific quinolones was detected in only 54.5% of the 55 patients tested, although some patients were tested up to 48 months after their initial adverse reaction. In this study, cross-reactivity based on the presence of quinolone-specific IgE to various quinolones, including pipemidic acid, nalidixic acid, pefloxacin, rufloxacin, cinoxacin, lomefloxacin, ciprofloxacin, norfloxacin, and ofloxacin was demonstrated; moxifloxacin was not tested. Moxifloxacin cross-reactivity has been looked at specifically in only one study. González et al.¹¹ used skin prick tests, intradermal tests, and oral challenges in 6 patients to determine cross-reactivity among 5 different fluoroquinolones: ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, and moxifloxacin. Of the 3 patients studied who had an initial reaction to moxifloxacin, only 1 reacted to oral challenges with ciprofloxacin and ofloxacin. The other 2 patients tolerated ciprofloxacin oral challenges and 1 of these patients also tolerated a levofloxacin oral challenge. Thus, clear conclusions on whether moxifloxacin cross-reacts with various other quinolones cannot be established.

Although González et al.¹¹ demonstrated positive oral challenge tests in several patients to a combination of moxifloxacin and ciprofloxacin, levofloxacin, or ofloxacin, 2 patients who reacted to oral challenge tests with moxifloxacin did not react to oral challenge tests with ciprofloxacin. This was similar to the results noted in our 3 patients, demonstrating a lack of cross-reactivity between ciprofloxacin and moxifloxacin for at least some patients. To the best of our knowledge, this is the first report of tolerance to full treatment courses of ciprofloxacin in patients who developed immediate hypersensitivity reactions to moxifloxacin. In the first and second patients, who had previously tolerated levofloxacin, it is possible that there is no cross-reactivity between moxifloxacin and levoflox-

acin, although we were unable to confirm this with a levofloxacin oral challenge. Based on these 3 cases and the results reported by Alemán et al.¹⁰ and González et al.,¹¹ it is highly plausible that, while some patients may react to a common fluoroquinolone ring structure and display cross-reactivity in oral challenge tests, others may react only to a side chain that is specific to moxifloxacin.

Specific side chain reactivity has been demonstrated with other antibiotics, such as the β -lactams. Over the past decade, a considerable amount of evidence has been gathered to establish that the immune response to cephalosporins is more dependent on their side chain structures. Studies using monoclonal antibodies have shown recognition of epitopes to specific side chains of the cephalosporins and not to the thiazolidine ring or the conjugated nuclear region of the penicillins.^{43,44} As well, rabbit antibodies against cephalosporins with different side chains have not been found to cross-react.⁴⁵

All fluoroquinolones consist of a bicyclic ring structure in which there is a substitution at position 1 with various moieties (Figure 1).⁵ Both ciprofloxacin and moxifloxacin have a cyclopropyl group in position 1 to enhance pharmacokinetic properties and gram-negative activity (Figures 2 and 3).^{2,46,47} Where moxifloxacin differs from ciprofloxacin is in positions 7 and 8; ciprofloxacin exhibits an unsubstituted 6-membered piperazine ring at position 7 that confers good gram-negative activity.^{2,46,47} Moxifloxacin, on the other hand, has a 5-membered diazabicyclic ring that confers gram-positive activity, especially toward *Streptococcus pneumoniae*.^{2,46,47} Furthermore, moxifloxacin has a methoxy group in position 8 to reduce photoreactivity and to enhance anaerobic activity.^{2,46,47} Ciprofloxacin does not have any side chain in this position. Based on the structural differences at positions 7 and 8, it is conceivable that there may be side chain reactivity to these sites alone. This would potentially explain the lack of cross-reactivity between ciprofloxacin and moxifloxacin in our patients. In patients who display cross-reactivity to ciprofloxacin and moxifloxacin, the reaction may be based on the general bicyclic structure of the molecule or on the cyclopropyl group at position 1.

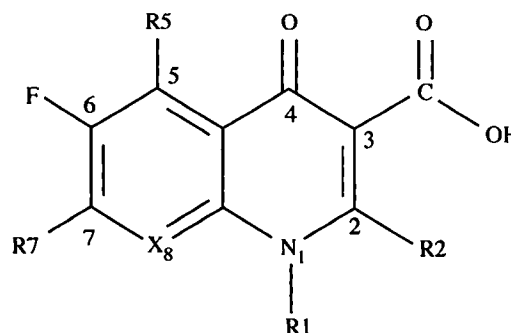


Figure 1. General structure of a fluoroquinolone.

Of interest, an analysis of spontaneous reports of fluoroquinolone-associated anaphylaxis in Germany showed that moxifloxacin accounted for 54% of these reports.¹² This rate is considerably higher than that of other fluoroquinolones. For example, levofloxacin accounted for only 15% of the reports and ciprofloxacin accounted for only 13% of the reports. The corresponding reporting rates per 1 million defined daily doses based on crude estimates of exposure were 3.3, 0.6, 0.2, and 0.2 for moxifloxacin, levofloxacin, ciprofloxacin, and ofloxacin, respectively. If side chain substitutions occurring at positions 7 and 8 have more antigenic potential for inciting hypersensitivity, then it is possible that moxifloxacin may have a higher occurrence rate for anaphylaxis. While the data presented in this analysis provide a signal that drug-associated anaphylaxis could occur more frequently with moxifloxacin when compared to other fluoroquinolones, appropriately designed epidemiologic studies, such as case-control studies, are required to address this hypothesis.

There are several limitations to our case series. First, our patients were not tested consistently over the course of a 5-year period due to changes in our testing protocol. Intradermal skin tests for moxifloxacin were not performed for all 3 patients because these tests have low sensitivity and often result in irritant reactions.^{7,8} Oral challenge tests, which were completed in all 3 patients, remain the gold standard for detecting hypersensitivity reactions. Therefore, the lack of intradermal skin test results for 2 of the patients likely had little impact on our overall conclusion. In addition, we were unable to contact the second patient to determine whether she continued to take treatment courses of ciprofloxacin after her

moxifloxacin oral challenge. This information would have strengthened our case series, but we feel that the likelihood of cross-reactivity is low, given this patient's tolerance of a full treatment course of ciprofloxacin after an initial anaphylactoid reaction to moxifloxacin. Finally, we did not conduct oral challenge tests with fluoroquinolones other than ciprofloxacin. For this reason, we cannot confirm whether our patients have a specific side chain reaction to moxifloxacin alone. Further research into this area is required to confirm the possibility of an immunologic reaction to a side chain that is unique to moxifloxacin.

In cases where patients have displayed an immediate hypersensitivity reaction to moxifloxacin but have clearly demonstrated tolerance to full treatment courses of ciprofloxacin, we believe that these patients will likely continue to tolerate ciprofloxacin. However, should ciprofloxacin therapy be required in the future, these patients should be treated in a monitored medical setting where possible, such as a drug safety clinic. Furthermore, these patients should be evaluated on an individual basis. Further research into whether there is a specific side chain reaction to moxifloxacin is warranted.

Brenda Chang BSc Pharm ACPR, at time of writing, PharmD Student, School of Pharmacy, University of Colorado, Denver, CO; now, Primary Care Pharmacist, Department of Family and Community Medicine and Department of Pharmacy, St. Michael's Hospital, Toronto, Ontario, Canada

Sandra R Knowles BScPhm ACPR, Drug Safety Pharmacist, Drug Safety Clinic and Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto; Department of Medicine, Division of Clinical Pharmacology and Toxicology, Sunnybrook Health Sciences Centre

Elizabeth Weber MD FRCPC, Staff Physician, Drug Safety Clinic, Sunnybrook Health Sciences Centre; Department of Medicine, Division of Clinical Pharmacology and Toxicology, Sunnybrook Health Sciences Centre

Reprints: Ms. Chang, Health Centre at 410, St. Michael's Hospital, 410 Sherbourne St., 3rd Floor, Toronto, Ontario M4X 1K2, Canada, fax 416/867-3726, changb@smh.toronto.on.ca

Financial disclosure: None reported

References

1. Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM. Quinolones in 2005: an update. *Clin Microbiol Infect* 2005;11:256-80. DOI 10.1111/j.1469-0691.2005.01131.x
2. Appelbaum PC, Hunter PA. The fluoroquinolone antibacterials: past, present and future perspectives. *Int J Antimicrob Agents* 2000;16:5-15. DOI 10.1016/S0924-8579(00)00192-8
3. Ball P. Adverse drug reactions: implications for the development of fluoroquinolones. *J Antimicrob Chemother* 2003;51(suppl 1):21-7. DOI 10.1093/jac/dkg209
4. Bertino J Jr, Fish D. The safety profile of the fluoroquinolones. *Clin Ther* 2000;22:798-817. DOI 10.1016/S0149-2918(00)80053-3
5. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. *Curr Med Chem* 2001;8:371-84.
6. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007;41:1859-66. DOI 10.1345/aph.1K347
7. Campi P, Fichler WJ. Quinolone hypersensitivity. *Curr Opin Allergy Clin Immunol* 2003;3:275-81. DOI 10.1097/00130832-200308000-00007
8. Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. *Curr Allergy Asthma Rep* 2005;5:15-21. DOI 10.1007/s11882-005-0049-1

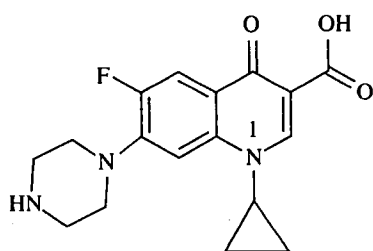


Figure 2. Ciprofloxacin.

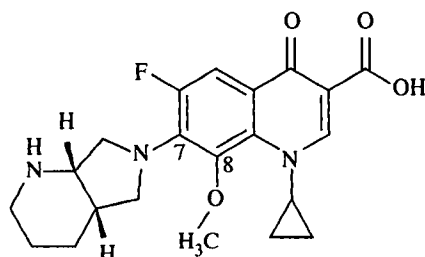


Figure 3. Moxifloxacin.

9. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin. *Drug Saf* 2009;32:359-78. DOI 10.2165/00002018-200932050-00001
10. Alemán AM, Quirce S, Cuesta J, Novalbos A, Sastre J. Anaphylactoid reaction caused by moxifloxacin. *J Investig Allergol Clin Immunol* 2002;12:67-8.
11. González I, Lobera T, Blasco A, del Pozo MD. Immediate hypersensitivity to quinolones: moxifloxacin cross-reactivity. *J Investig Allergol Clin Immunol* 2005;15:146-9.
12. Sachs B, Riegel S, Seebeck J, et al. Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Saf* 2006;29:1087-100. DOI 10.2165/00002018-200629110-00008
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
14. Kothur K, Singh M, Dayal D. Ciprofloxacin-induced anaphylactoid reaction. *Eur J Pediatr* 2006;165:573-4. DOI 10.1007/s00431-006-0099-y
15. Ho DY, Song JC, Wang CC. Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003;37:1018-23. DOI 10.1345/aph.1C498
16. Burke P, Burne SR. Allergy associated with ciprofloxacin. *BMJ* 2000;320:679. DOI 10.1136/bmj.320.7236.679
17. Erdem G, Staat MA, Connelly BL, Assa'ad A. Anaphylactic reaction to ciprofloxacin in a toddler: successful desensitization. *Pediatr Infect Dis J* 1999;18:563-4. DOI 10.1097/00006454-199906000-00022
18. Clutterbuck DJ, McMillan A. Anaphylactoid reaction to ciprofloxacin. *Int J STD AIDS* 1997;8:707-8. DOI 10.1258/0956462971918931
19. Salon EJ, Newbrough MA, Albarracín CA, Hernández JE. Anaphylactoid reaction to ciprofloxacin versus toxic shock syndrome (letter). *Ann Pharmacother* 1997;31:119-20.
20. Vidal C, Suarez J, Martínez M, González-Quintela A. Ciprofloxacin-induced glottic angioedema (letter). *Postgrad Med J* 1995;71:318. DOI 10.1136/pgmj.71.835.318-a
21. Assouad M, Willcourt RJ, Goodman PH. Anaphylactoid reactions to ciprofloxacin (letter). *Ann Intern Med* 1995;122:396-7.
22. Soetikno RM, Johnson JL, Carey JT. Ciprofloxacin-induced anaphylactoid reaction in a patient with AIDS (letter). *Ann Pharmacother* 1993;27:1404.
23. Deamer RL, Prichard JG, Loman GJ. Hypersensitivity and anaphylactoid reactions to ciprofloxacin. *Ann Pharmacother* 1992;26:1081-4.
24. Berger TG, Franklin N. Anaphylactoid reaction to ciprofloxacin in a patient infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1992;26:256-7. DOI 10.1016/S0190-9622(08)80302-7
25. Miller MS, Gaido F, Rourke MH Jr, Spock A. Anaphylactoid reactions to ciprofloxacin in cystic fibrosis patients. *Pediatr Infect Dis J* 1991;10:164-5. DOI 10.1097/00006454-199102000-00020
26. Kennedy CA, Goetz MB, Mathisen GE. Ciprofloxacin-induced anaphylactoid reactions in patients infected with the human immunodeficiency virus (letter). *West J Med* 1990;153:563-4.
27. Davis H, McGoodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989;111:1041-3.
28. Wurtz RM, Abrams D, Becker S, Jacobson MA, Mass MM, Marks SH. Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients (letter). *Lancet* 1989;1:955-6. DOI 10.1016/S0140-6736(89)92529-4
29. Peters B, Pinching AJ. Fatal anaphylaxis associated with ciprofloxacin in a patient with AIDS related complex (letter). *BMJ* 1989;298:605. DOI 10.1136/bmj.298.6673.605-b
30. Baciiewicz AM, Georges G, Becker M, Schnall AM. Laryngeal edema related to ciprofloxacin therapy (letter). *Ann Pharmacother* 1992;26:1456.
31. Burks EJ. Norfloxacin hypersensitivity (letter). *DICP* 1989;23:90.
32. Desai C, Desai KJ, Shah UH. Ofloxacin induced hypersensitivity reaction. *J Assoc Physicians India* 1999;47:349.
33. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000;20:1520-3. DOI 10.1592/phco.20.19.1520.34868
34. Takahama H, Tsutsumi Y, Kubota Y. Anaphylaxis due to levofloxacin. *Int J Dermatol* 2005;44:789-90. DOI 10.1111/j.1365-4632.2004.02325.x
35. González-Mancebo E, Fernández-Rivas M. Immediate hypersensitivity to levofloxacin diagnosed through skin prick test (letter). *Ann Pharmacother* 2004;38:354. DOI 10.1345/aph.1D159
36. Stricker BH, Slagboom G, Demaesseneer R, Sloatmaekers V, Thijs I, Olsson S. Anaphylactic reactions to cinoxacin. *BMJ* 1988;297:1434-5. DOI 10.1136/bmj.297.6661.1434
37. Valdivieso R, Pola J, Losada E, Subiza J, Armentia A, Zapata C. Severe anaphylactoid reaction to nalidixic acid. *Allergy* 1988;43:71-3. DOI 10.1111/j.1398-9995.1988.tb02046.x
38. Dávila I, Díez ML, Quirce S, Fraj J, De La Hoz B, Lazaro M. Cross-reactivity between quinolones. Report of three cases. *Allergy* 1993;48:388-90. DOI 10.1111/j.1398-9995.1993.tb02413.x
39. al-Hedaithy MA, Noreddin AM. Hypersensitivity anaphylactoid reaction to pefloxacin in a patient with AIDS. *Ann Pharmacother* 1996;30:612-4.
40. Umebayashi Y, Furuta J. Anaphylaxis due to tosufloxacin tosylate (letter). *J Dermatol* 2003;30:701-2.
41. Blayac JP, Hillaire-Buys D, Pinzani V. Fluoroquinolones and anaphylaxis. *Thérapie* 1996;51:417-8.
42. Manfredi M, Severino M, Testi S, et al. Detection of specific IgE to quinolones. *J Allergy Clin Immunol* 2004;113:155-60. DOI 10.1016/j.jaci.2003.09.035
43. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 2005;115:1048-57. DOI 10.1542/peds.2004-1276
44. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. *Diagn Microbiol Infect Dis* 2007;57:13S-8S. DOI 10.1016/j.diagmicrobio.2006.12.004
45. Kelkar PS, Li JT. Cephalosporin allergy. *N Engl J Med*. 2001;345:804-9. DOI 10.1056/NEJMra993637
46. Andersson MI, MacGowan AP. Development of the quinolones. *J Antimicrob Chemother* 2003;51(suppl 1):1-11. DOI 10.1093/jac/dkg212
47. Higgins PG, Fluit AC, Schmitz FJ. Fluoroquinolones: structure and target sites. *Curr Drug Targets* 2003;4:181-90. DOI 10.2174/1389450033346920