

Cutaneous Adverse Reactions to Fluoroquinolones

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Background: To date, even though there are some large studies on adverse reactions related to fluoroquinolones, there is no comprehensive study focusing on cutaneous adverse drug reactions associated with their use.

Objective: To demonstrate the pattern of cutaneous reaction related to the administration of each type of fluoroquinolone and to study the cross-sensitivity between various types of fluoroquinolones.

Methods: Voluntary reports of any adverse events associated with fluoroquinolone use as reported from January 2004 to December 2008 and obtained from the Adverse Drug Reaction Center, Siriraj Hospital, Thailand, were reviewed.

Results: Among 166,736 patients who had been treated with fluoroquinolones, the prevalences of adverse reaction and cutaneous adverse reaction were 0.13% and 0.09%, respectively. The prevalence of cutaneous reaction to individual fluoroquinolones varies between 0.04% and 0.37%. One hundred fifty-one subjects were enrolled. Most cutaneous reactions were attributed to ciprofloxacin ($n = 93$), and the most frequent adverse cutaneous reaction seen was maculopapular rash (39.7%). Thirteen cases (8.6%) involved a previous history of fluoroquinolone hypersensitivity; among these, 15.4% had cross-reactivity potential.

Conclusion: These data suggest that individual fluoroquinolones are responsible for different types and frequencies of cutaneous reactions, with some potentiality of cross-reactivity between different generations.

FLUOROQUINOLONES are broad-spectrum and widely prescribed antibiotics.^{1–3} Quinolones may be categorized into four generations based on their antibacterial properties and their chemical structures. The first generation includes pipemidic acid, whereas the second includes norfloxacin, ofloxacin, and ciprofloxacin. Levofloxacin and gatifloxacin are the members of the third-generation group, and moxifloxacin is part of the fourth-generation group.⁴ As a result of the distinct physicochemical structure of specific agents, the incidence of adverse reactions varies.⁵ The adverse effects that are associated with fluoroquinolone use are most commonly gastrointestinal disturbances ($> 3\%$), cutaneous reactions ($< 2.5\%$), and central nervous system effects (1–2%).^{2,5} Although most adverse events are usually mild and self-limited, serious and life-threatening adverse events such as anaphylaxis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported.^{2,5–8}

To date, although a limited number of studies on adverse drug reactions caused by fluoroquinolones have

been published, no comprehensive study focusing on cutaneous adverse drug reactions associated with fluoroquinolone use has ever been performed. Therefore, the purpose of this study was to demonstrate the pattern of cutaneous reaction related to the administration of each type of fluoroquinolone and to study the cross-sensitivity between various types of fluoroquinolones.

Methods

Patients and Study Design

This retrospective study was approved by the Ethics Committee of the Siriraj Institute Review Board, Siriraj Hospital, Mahidol University, and was performed at Siriraj Hospital, a medical school and tertiary referral center in Thailand.

Patients 18 years of age and older were included. Cutaneous adverse reactions (with or without systemic symptoms) to fluoroquinolones were diagnosed and voluntarily reported to the Adverse Drug Reaction (ADR) Center by attending physicians and dermatologists. Well-trained and experienced ADR Center pharmacists and dermatologists then reviewed the event and assessed the causative agents based on history, clinical manifestation, and laboratory data. Drug imputability of the cases was classified into six levels (certain, probable,

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possible, unlikely, unclassified, and unclassifiable) according to World Health Organization Uppsala Monitoring Centre guidelines.⁹

For this study, reports of any adverse events from inpatients and outpatients associated with fluoroquinolone use that were reported from January 2004 to December 2008 were obtained from the ADR Center at Siriraj Hospital.

Statistical Analysis

Descriptive statistics were used for demographic data, cutaneous adverse drug reactions, and clinical characteristics. Data on SJS and TEN for patients positive and negative for human immunodeficiency virus (HIV) were compared by using the Fisher exact test. Demographic and clinical data on patients with and without maculopapular rash or urticaria or angioedema were compared with the Pearson chi-square test and the Mann-Whitney *U* test for qualitative and quantitative data, respectively. All statistical data analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Among 166,736 patients who were treated with fluoroquinolones during our 5-year study period, 216 patients were suspected of having had an adverse drug reaction associated with fluoroquinolone administration. Of these, 65 patients were excluded because they were younger than 18 years or did not have a cutaneous manifestation. Therefore, 151 patients were included in the study. The prevalences of adverse reaction and cutaneous adverse reaction were 0.13% and 0.09%, respectively. The prevalence of cutaneous reaction to an individual fluoroquinolone was 0.37% for ciprofloxacin, 0.1% for moxifloxacin, 0.07% for gatifloxacin, 0.06% for levofloxacin, and 0.04% for both ofloxacin and norfloxacin. One hundred fifty-four drugs were suspected of causing cutaneous reactions associated with fluoroquinolone use. Table 1 shows the demographic and clinical data of the participants. Sixty-three (41.7%) were men, 88 (58.3%) were women, and the mean age was 51.1 years (range, 19–90 yr). Of 83 patients whose data on atopy were accessible, 52 (62.7%) had a history of atopic diathesis, especially allergic rhinitis (35 of 83 patients [42.2%]). Eight (5.3%) of the 151 subjects had a positive history of food intolerance; of these, 6 patients were reported to react to shrimp. Sixty-three patients were tested for HIV infection; 16 (10.6%) proved to be HIV

Table 1. Demographic and Clinical Data of Patients with Cutaneous Adverse Reactions to Fluoroquinolones

Characteristic	No. (%) of Patients* (n = 151)
Male	63 (41.7)
Female	88 (58.3)
Personal history of atopy	52 (34.4)
Family history of atopy	11 (7.3)
History of food allergy	8 (5.3)
History of adverse drug reaction (including fluoroquinolones)	74 (49)
History of adverse reaction to fluoroquinolones	13 (8.6)
Underlying disease	
Hypertension	34 (22.5)
Dyslipidemia	27 (17.9)
Diabetes mellitus	15 (9.9)
Ischemic heart disease	12 (7.9)
Renal failure	11 (7.3)
Systemic lupus erythematosus	9 (6.0)
Prostate cancer	5 (3.3)
HIV infection	16 (10.6)

HIV = human immunodeficiency virus.

*Mean age: 51.1 ± 19.1 years.

positive. The most common underlying diseases were hypertension in 34 patients (22.5%), dyslipidemia in 27 patients (17.9%), and diabetes mellitus in 15 patients (9.9%). One hundred eight patients (71.5%) had received only one medication before the adverse events occurred. A probable diagnosis was made for 52 patients (34.4%), and a possible diagnosis was made for 99 subjects (65.6%).

Most cutaneous reactions were attributed to ciprofloxacin (*n* = 93 [60.4%]), and the most frequent adverse cutaneous reaction seen was maculopapular rash (39.7%). Other types of adverse cutaneous eruptions and their responsible agents are listed in Table 2.

Severe reactions such as SJS or TEN (SJS/TEN) were reported in 14 patients, all of whom were given the drug in oral form. The reactions occurred between 1 and 19 days after the drug had been taken. Eleven of 14 patients were hospitalized, and the mean duration of hospital stay was 21 days (range, 5–75 days). Seven patients were reported to have had an anaphylactic reaction to fluoroquinolones. Four of these patients were given the drug in oral form; the drug was administered intravenously to the others. All reactions occurred within 2 days after the first dose. Anaphylaxis on the first day was reported in 5 of the 7 patients (71.4%); 3 of the 5

Table 2. Cutaneous Adverse Drug Reactions to Different Types of Fluoroquinolones

Reaction	Nor	O	Cipro	Levo	Gati	Moxi	Ru	No. (%) of Reactions (n = 151)
Maculopapular rash	2	10*	40*	8*	1	1	0	60 (39.7)
Angioedema and/or urticaria	10	4	20	5	1	1	0	40 (26.5)
Angioedema alone	5	1	5	0	0	0	0	11 (7.3)
Urticaria alone	4	2	12*	5	1*	1	0	24 (15.9)
Angioedema and urticaria	1	1	3	0	0	0	0	5 (3.3)
SJS/TEN	2	4	5	1	0	1	1	14 (9.3)
Injection-site reaction	0	0	8	0	0	0	0	8 (5.3)
Nonspecific eczema	4	0	3	0	0	0	0	7 (4.6)
Anaphylaxis	0	1	6	0	0	0	0	7 (4.6)
Fixed drug eruption	2	2	2	0	0	0	0	6 (4.0)
Erythroderma	0	0	4	0	0	0	0	4 (2.6)
Erythema multiforme	0	0	2	0	0	0	0	2 (1.3)
Urticarial vasculitis	0	0	1	0	0	0	0	1 (0.7)
Drug hypersensitivity syndrome	0	0	1	0	0	0	0	1 (0.7)
Lichenoid drug eruption	0	0	1	0	0	0	0	1 (0.7)

Cipro = ciprofloxacin; Gati = gatifloxacin; Levo = levofloxacin; Moxi = moxifloxacin; Nor = norfloxacin; O = ofloxacin; Ru = rufloxacin; SJS/TEN = Stevens-Johnson syndrome or toxic epidermal necrolysis.

*Two agents were suspected of causing one reaction.

patients whose anaphylaxis occurred on the 1st day had had no prior exposure to fluoroquinolones. In our study, none of the 151 subjects experienced a fatal outcome related to a fluoroquinolone hypersensitivity reaction, and most patients recovered after the discontinuation of the drug together with symptomatic and supportive treatment. One hundred six patients were treated with antihistamines, while short-course systemic corticosteroids were given to 37 patients. The dosages of dexamethasone and prednisolone ranged from 4 to 30 mg per day and from 5 to 40 mg per day, respectively.

Regarding specific groups of cutaneous reactions (ie, maculopapular rash and urticaria and/or angioedema), the data show no statistically significant association between a patient's background (demographic data, atopic diathesis, underlying diseases, HIV status, history of previous drug allergy, and type of fluoroquinolone taken) and any one of these reactions.

As seen in 63 cases with available data on HIV status, there were significantly more urticarial eruptions among HIV-negative patients than in the HIV-positive group. In contrast, SJS/TEN events occur more in HIV-positive groups than in HIV-negative groups. Other manifestations are described in Table 3.

Seventy-four patients had a positive history of adverse drug reactions. Thirteen patients (8.6%) had a history of fluoroquinolone hypersensitivity; among these patients,

7 patients were reported to have had the reaction to the drug within the generation. On the other hand, 15.4% had cross-reactivity potential (Table 4 and Table 5).

Table 3. HIV Status and Adverse Drug Reactions

Adverse Drug Reaction	HIV Status (n = 63)		p Value
	Positive (n = 16)	Negative (n = 47)	
Maculopapular rash	9	15	0.070
Angioedema and/or urticaria	0	18	0.003*
Angioedema alone	0	6	0.324
Urticaria alone	0	11	0.052
Angioedema and urticaria	0	1	1.000
SJS/TEN	5	4	0.039*
Fixed drug eruption	1	2	1.000
Anaphylaxis	0	3	0.564
Nonspecific eczema	0	2	1.000
Injection-site reaction	0	2	1.000
Drug hypersensitivity syndrome	0	1	1.000
Lichenoid drug eruption	1	0	0.254
Erythema multiforme	0	1	1.000
Urticarial vasculitis	0	1	1.000
Erythroderma	0	0	—

SJS/TEN = Stevens-Johnson syndrome or toxic epidermal necrolysis.

*Significant p value.

Table 4. Patients with History of Drug Hypersensitivity

<i>Agents Causing Previous Adverse Reactions</i>	<i>No. (%) of Drugs (n = 74)</i>
Penicillin	25 (33.8)
Sulfonamide	14 (18.9)
Fluoroquinolones	13 (17.6)
Ciprofloxacin	7 (9.5)
Norfloxacin	4 (5.4)
Ofloxacin	1 (1.4)
Levofloxacin	1 (1.4)
Gatifloxacin	1 (1.4)
Cephalosporin	12 (16.2)
Macrolide	5 (6.8)
Rifampicin	5 (6.8)
Nonsteroidal antiinflammatory drugs	4 (5.4)
Isoniazid	4 (5.4)
Tetracycline	3 (4.1)
Imipenem	3 (4.1)
Antiretroviral drugs	3 (4.1)
Aminoglycoside	3 (4.1)
Phenytoin	3 (4.1)
Pyrazinamide	2 (2.7)
Amikacin	2 (2.7)
Clindamycin	2 (2.7)
Metronidazole	2 (2.7)
Vancomycin	2 (2.7)
Piperacillin-tazobactam	1 (1.4)
Colistin	1 (1.4)

Discussion

Puavilai and colleagues, who studied 212 patients in Bangkok who developed drug eruptions from any drugs, reported maculopapular rash to be of the highest frequency among those with drug eruptions from fluoroquinolones (2 of 7 cases).¹⁰ Our study also revealed that the most common form of cutaneous reaction to fluoroquinolones is an exanthematous reaction followed by urticaria and/or angioedema. On the other hand, Campi and Pichler reviewed 384 case reports of any adverse reaction to quinolones and stated that immediate adverse reactions such as urticaria, angioedema, and anaphylactic shock were most frequently described.¹¹ The drug's safety and efficacy vary among patients, owing to their differing genetic makeups.¹²

The exanthematous reaction can occur at any time after the first dose of the treatment¹³ (there was a range of within 24 hours to 43 days in our study). Like patients who react to trimethoprim-sulfamethoxazole,^{14,15} HIV-infected

patients seem to be at significantly increased risk of developing SJS/TEN with fluoroquinolones. Previous data indicated that drugs that are started less than 7 days or more than 2 months before a reaction are unlikely to be responsible for SJS/TEN.¹³ However, in our 7 (50%) out of 14 SJS/TEN patients the suspected fluoroquinolones were given within 1 week prior to the reaction. Nevertheless, the route of administration and the difficulty of firmly diagnosing adverse drug reaction and determining the responsible drug in an adverse event^{13,16} (especially if more than one medication has been administered) may complicate analysis, leading to discrepant results.

Referring to a study of 166 cases of fluoroquinolone-associated anaphylaxis,¹⁷ Sachs and colleagues reported that the route of administration of fluoroquinolones was predominantly oral (160 of 166 reports). Our study, however, showed no polarity.

Lapi and colleagues reported that ciprofloxacin is responsible for the highest proportion of cutaneous reactions, whereas moxifloxacin has the highest rate of adverse reaction reports (84.6 reports per defined daily dose per 1,000 inhabitants per day).¹⁸ Our study shows supportive data indicating that ciprofloxacin accounts for the majority (60.4%) of adverse cutaneous reactions to fluoroquinolones.

According to a study of atopy and drug allergy,¹⁹ atopic diathesis is not a predisposing factor for drug allergy. Even in the case of urticaria and angioedema, which were previously described as type I (immunoglobulin E-mediated) hypersensitivity mechanism,²⁰ our study found no association between patients' atopic diathesis and these specific types of reactions.

Our study showed that 6 of 8 patients who had a cutaneous reaction to fluoroquinolones and also had a food intolerance had a cutaneous reaction upon ingesting shrimp. Some studies state that quinolones have been commonly used as an antibiotic by shrimp cultivators in Southeast Asia and can be detected in food products as residues.²¹ However, the association of antibiotic residues in food products and food intolerance should be further investigated beyond anecdotal evidence.

Davila and colleagues reported on three patients who developed cross-reactivity after oral controlled provocation testing with the opposite generation of fluoroquinolone.²² Gonzalez and colleagues⁴ described six patients with immediate hypersensitivity to different types of quinolones and for whom the result of a single-blind moxifloxacin oral challenge test was immediately positive. However, the result differed from those of other quinolone challenge tests administered to the suspected moxifloxacin-hypersensitivity

Table 5. Cross-Reactivity between Various Types of Fluoroquinolones

Suspected Drug in This Study (n = 154)	Patients with History of Fluoroquinolone Hypersensitivity (n = 13)						Cross-Reactions			
	Second Generation			Third Generation		Fourth Generation	Within Group	Across Group	Total	Proportion of Cross-Reactivity
	Nor	O	Cipro	Levo	Gati	Moxi				
Norfloxacin (n = 20)	1*	0	2	1	0	0	2	1	3	3/20 (15.0%)
Ofloxacin (n = 21)	2	0	0	0	0	0	2	0	2	2/21 (9.5%)
Ciprofloxacin (n = 93)	1	1	5*	0	0	0	2	0	2	2/93 (2.2%)
Levofloxacin (n = 14)	0	0	0	0	1	1	1	1	2	2/14 (14.3%)
Gatifloxacin (n = 2)	0	0	0	0	0	0	0	0	0	0/2
Moxifloxacin (n = 3)	0	0	0	0	0	0	0	0	0	0/3
Rufloxacin (n = 1)	0	0	0	0	0	0	0	0	0	0/1

Cipro = ciprofloxacin; Gati = gatifloxacin; Levo = levofloxacin; Moxi = moxifloxacin; Nor = norfloxacin; O = ofloxacin.

*Minor cutaneous eruptions associated with fluoroquinolone intake occurred prior to this event but were not recognized as drug eruptions by patient. Physicians had not been informed about these reactions before prescribing the medications.

group. Our study showed that 13 of 151 patients had a previous history of hypersensitivity to fluoroquinolones. During the course of the study, there were seven cases of generation-specific reaction, whereas cross-reactivity between generations was suspected in two cases. These results imply that all quinolones should be used with caution owing to the possibility of cross-reactivity between different fluoroquinolones even within the same generation or across different generations.

A previous publication proposed that the extent of cross-reactivity among different quinolones depends on the type of clinical manifestation and its underlying mechanism.²³ Specific serum immunoglobulin E to more than one quinolone can be demonstrated among patients with immediate-type (type 1) cross-reactivity. Fluoroquinolone-specific T-cell clones also play a major role in delayed maculopapular exanthemas.¹² However, our study showed no statistically significant association between previous type of cutaneous reaction and current cutaneous manifestation.

To our knowledge, the role of corticosteroids in the management of SJS/TEN is controversial.^{24–27} This study showed that the duration of hospital stay was shorter for patients who had been treated with systemic corticosteroids (8.5 ± 2.4 days and 35.5 ± 28.1 days, respectively, for

SJS/TEN patients who had been treated with and without intravenous dexamethasone). It should be noted that we had only a small number of patients with SJS/TEN. A larger controlled study is needed.

Although there is a previous report of 142 cases of fluoroquinolone-induced photosensitivity,²⁸ no photosensitive eruption was observed in our study. However, the major responsible drugs found in the previous report are enoxacin, lomefloxacin, tosufloxacin, fleroxacin, and sparfloxacin, which are different from the drugs reported in our study.

Because our findings are based on voluntary reporting data from physicians and patients, there may be some underreporting biases. At Siriraj Hospital, however, a history of adverse drug reaction is routinely taken by pharmacists before the distribution of any single medication, which can minimize underreporting biases from physicians. Patients are asked to come back for follow-up sessions every time antibiotics are used for infectious diseases; thus, underreporting biases from patients are minimized.

Conclusion

Our data suggest that individual fluoroquinolones are responsible for different types and frequencies of

cutaneous reactions with the potential of cross-reactivity between different generations. Although the results of this study show no statistical differences because of the limited number of subjects, a larger well-controlled trial is needed to reveal more details about cutaneous adverse reactions to fluoroquinolones.

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