

## ORIGINAL ARTICLE

## Diagnostic testing in suspected fluoroquinolone hypersensitivity

C. S. Seitz<sup>1,2</sup>, E. B. Bröcker<sup>1</sup> and A. Trautmann<sup>1</sup><sup>1</sup>Department of Dermatology, Venereology and Allergology, University of Würzburg, Germany and <sup>2</sup>Department of Dermatology, Venereology and Allergology, University of Göttingen, GermanyClinical &  
Experimental  
Allergy

## Summary

**Background** Because of their broad antibacterial activity in the gram-negative and gram-positive spectrum, high oral bioavailability, and good tissue penetration, fluoroquinolone antibiotics are widely used. Besides direct drug-related side-effects, fluoroquinolones may cause hypersensitivity reactions.

**Objective** The aim of this retrospective analysis was to present the results of diagnostic testing in cases of clinically suspected fluoroquinolone-induced immediate or delayed hypersensitivity.

**Methods** We studied 101 patients with a history of immediate or delayed hypersensitivity symptoms in temporal relation to treatment with a fluoroquinolone antibiotic using standardized skin testing, followed by oral challenges. Patients with anaphylaxis symptoms were further evaluated with *in vitro* tests.

**Results** Fluoroquinolone hypersensitivity was excluded in 71 patients by tolerated oral challenge tests. During positive challenge tests, six patients (three out of these had positive and three had negative skin prick tests) developed anaphylaxis symptoms but the presumed IgE-mediated mechanism could not be confirmed by *in vitro* tests. Patch testing was constantly negative; however, in two patients a rash was induced by the challenge tests.

**Conclusion** History alone leads clearly to a considerable over-estimation of fluoroquinolone hypersensitivity. Moreover, skin or *in vitro* tests do not seem to be very useful in identifying hypersensitive patients. Challenge tests appear to be necessary for definitely confirming or ruling out fluoroquinolone hypersensitivity.

**Keywords** anaphylaxis, challenge test, exanthema, provocation test, skin test, urticaria

*Submitted 9 April 2009; revised 23 June 2009; accepted 1 July 2009*

## Correspondence:

A. Trautmann, Department of Dermatology, Venereology and Allergology, University of Würzburg, Josef Schneider Strasse 2, 97080 Würzburg, Germany.

E-mail:

trautmann\_a@klinik.uni-wuerzburg.de

## Introduction

The fluoroquinolones ciprofloxacin, ofloxacin, and levofloxacin (an enantiomer of ofloxacin) are DNA-gyrase inhibitors with a broad antibacterial spectrum including gram-negative (*Salmonella*, *Pseudomonas*) as well as some gram-positive bacteria such as *Enterobacter* and *Haemophilus* [1]. They may be indicated for urinary tract infection, lower respiratory tract infection, or skin and soft tissue infection. Additionally, moxifloxacin is used in suspected anaerobic infections and in nosocomial pneumonia. Fluoroquinolones have few adverse effects, most commonly affecting the gastrointestinal system (nausea) and central nervous system (headache, dizziness, confusion). Less common but more serious adverse events include prolongation of the QT interval, phototoxicity, liver enzyme abnormalities, arthropathy, and cartilage and tendon abnormalities [1, 2]. Immediate and delayed hypersensitivity reactions to

fluoroquinolones have been observed in clinical trials and were recognized relatively frequently in drug reaction reports [3, 4]. Anaphylaxis seems to account for the majority of these reactions, whereas both non-immune mediated as well as IgE-mediated mechanisms were assumed [5, 6]. Maculopapular exanthemata, hypersensitivity syndrome with internal organ involvement, and bullous skin reactions have also been reported [7–9].

Fluoroquinolone hypersensitivity may be suspected when (i) the symptoms and physical findings are compatible with an immediate or a delayed hypersensitivity reaction; (ii) there is a definite temporal relationship between administration of the fluoroquinolone and the hypersensitivity reaction; and (iii) there is no other clear cause for the symptoms [10]. Skin tests may be used for the evaluation of suspected fluoroquinolone hypersensitivity. However, there are only limited data in the literature of positive patch tests with fluoroquinolones, and prick and intradermal tests

were either negative or considered as unreliable due to positive reactions in the control group [7, 11]. Therefore, the most prudent way of establishing the diagnosis of fluoroquinolone hypersensitivity has been a standardized challenge test [12].

The aim of this retrospective analysis was to evaluate the reliability of a diagnostic procedure including skin, *in vitro*, and oral challenge tests for definite identification of fluoroquinolone hypersensitivity and to obtain evidence for the causal pathomechanism of the hypersensitivity reaction.

## Material and methods

### Patients

From 2000 to 2008, all patients referred to our allergy clinic with a suggestive history of a fluoroquinolone-induced hypersensitivity reaction who had been skin tested with fluoroquinolones were retrospectively identified. After a thorough review of patient files all available clinical data were collected. The reported anaphylaxis symptoms were classified according to severity (Table 1) [13]. Grade 1 consists of cutaneous symptoms such as urticaria and angioedema; grades 2 and 3 include symptoms of the following organ systems: cardiovascular (hypotension, tachycardia), respiratory (dyspnoea, bronchoconstriction), and digestive (vomiting, abdominal pain, incontinence). As part of the standard practice in our allergy clinic, all subjects had been informed of any risks involved with the testing and written informed consent for allergologic work-up (skin tests, *in vitro* tests, oral challenge) had been obtained. Since determination of potential drug allergy is part of routine diagnostic practice in our clinic, further ethical approval was not required.

### Skin tests

In patients with immediate hypersensitivity symptoms, we initially performed both prick and intradermal tests on the volar forearm with ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin according to international standards [14].

Table 1. Grading system for anaphylaxis (modified from [13])

| Grade                                                                                          | Symptoms                                                                                                                         |
|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 1 (mild): skin and subcutaneous tissue only                                                    | Generalized urticaria, periorbital oedema, or angioedema                                                                         |
| 2 (moderate): features suggesting respiratory, cardiovascular, or gastrointestinal involvement | Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), tachycardia, chest or throat tightness, or abdominal pain   |
| 3 (severe): hypoxia, hypotension, or neurological compromise                                   | Cyanosis, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence |

However, because we were unable to identify definite non-irritating test concentrations in 19 patients and even in controls, we abandoned intradermal testing. For prick tests parenteral fluoroquinolone preparations were used at a therapeutic concentration, i.e. ciprofloxacin (2 mg/mL), ofloxacin (2 mg/mL), levofloxacin (5 mg/mL), and moxifloxacin (1.6 mg/mL), respectively. All agents were freshly reconstituted, and a physiological saline solution was used as a negative control. After 20 min, the prick test was defined as positive if the weal diameter was >3 mm. In patients with delayed hypersensitivity symptoms, additional patch tests, either lesional (in case of fixed drug eruption) or on the upper back, were performed with the panel of fluoroquinolones at least 6 weeks after clearance of the skin rash. For patch testing, fluoroquinolone tablets (250 mg ciprofloxacin, 200 mg ofloxacin, 250 mg levofloxacin, and 400 mg moxifloxacin) were ground in a mortar and suspended with 1 mL physiological saline solution. Finn-chambers with an inside diameter of 8 mm and a height of 0.4 mm were filled with 1 drop of this suspension, i.e. approximately 20–30 µL. Patches were removed after 1 day and patch and prick test sides were evaluated for late reactions after 2, 3, and 4 days. In individual cases, hypersensitivity to drugs administered concomitant with the fluoroquinolone (e.g. other antimicrobial drugs, non-steroidal anti-inflammatory drugs) were excluded as potential triggers of the hypersensitivity reaction by additional skin and challenge tests.

### Tryptase measurement

Commercially available ImmunoCAP<sup>TM</sup> Tryptase (Phadia GmbH, Freiburg, Germany), an *in vitro* test for the quantitative measurement of tryptase concentration in human serum, was used [15].

### Basophil activation test

The basophil activation test (BAT), also called the flow-cytometric cellular allergen stimulation test (Flow-CAST), is based on the *in vitro* allergen-induced specific activation of basophils [16]. The assay was performed as described previously in detail [17]. Parenteral fluoroquinolone stock preparations (i.e. 2 mg/mL ciprofloxacin, 2 mg/mL ofloxacin, 5 mg/mL levofloxacin, and 1.6 mg/mL moxifloxacin) were used in 1 : 10, 1 : 100, and 1 : 1.000 dilutions. Drugs usually give lower basophil activation percentages than inhalant, food, or hymenoptera allergens [18]. Therefore, to obtain an optimal sensitivity and specificity, a cut-off value of 5% was applied so far as the negative control was maximally less than 2.5%.

### Oral challenge

Patients were offered oral challenge tests according to an established protocol using standardized single

Table 2. Doses for oral challenge tests with fluoroquinolones

| Fluoroquinolone | Doses (mg) |        |       |        |
|-----------------|------------|--------|-------|--------|
|                 | First      | Second | Third | Fourth |
| Ciprofloxacin   | 50         | 125    | 250   | 500    |
| Ofloxacin       | 25         | 50     | 100   | 200    |
| Levofloxacin    | 50         | 125    | 250   | 500    |
| Moxifloxacin    | 25         | 50     | 100   | 200    |

fluoroquinolone doses as shown in Table 2. The general principles of our challenge protocol were as follows [12, 19]: (i) the time interval since the hypersensitivity reaction was at least 6 weeks, (ii) during the entire challenge procedure the patient was observed and equipment for emergency treatment was available, (iii) the dosage of the fluoroquinolone increased stepwise to a normal dose with intervals of 1 h between the individual doses, (iv) strict adherence to absolute and relative contraindications for drug challenge tests, and (v) before challenge testing, written informed consent was obtained from each patient.

## Results

### Patients

A total of 101 patients were included in the analysis. All patients were referred by health care professionals, i.e. general practitioners, consultants, or allergologists, all suspecting fluoroquinolone hypersensitivity. The average age of the subjects (81 females and 20 males) at the time of the suspected fluoroquinolone-induced hypersensitivity reaction was 52 years (ranging from 18 to 87 years). Twenty-five patients (24.8%) were considered atopic due to a positive skin prick test (SPT) with aeroallergens or a history of atopic dermatitis, rhinitis, or asthma. In the vast majority, the fluoroquinolone was administered orally ( $n = 94$ ), and in seven patients intravenously. In Table 3, clinical data including underlying infectious disease and latency of the reaction (i.e. time between the start of the treatment and the onset of symptoms) are summarized. Depending on the latency between administration of the fluoroquinolone and the onset of symptoms, we classified the reactions as immediate in 64 and as delayed in 37 patients. A definite previous exposure to a fluoroquinolone without any adverse reaction was identifiable in 41 patients. Figure 1 shows the type and severity of the symptoms and the incriminated fluoroquinolones. The severity of anaphylaxis was graded according to Table 1. History of delayed reactions included maculopapular exanthema (29×), fixed drug eruption (7×), and one patient with acute generalized exanthematous pustulosis classified as having hypersensitivity syndrome (also called DRESS: drug reaction with eosinophilia and systemic symptoms) due to accompanied fever, lymphadenopathy, and elevated liver enzymes; severe generalized bullous skin reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis were not observed.

Table 3. Clinical data of the 101 patients studied

|                                          |            |
|------------------------------------------|------------|
| Age, mean (range) (y)                    | 52 (18–87) |
| Sex (male/female)                        | 20/81      |
| Indication for treatment; infection of:  |            |
| Upper and lower respiratory tract        | 42         |
| Genitourinary tract                      | 41         |
| Skin and soft tissue                     | 18         |
| Immediate hypersensitivity, i.e. latency |            |
| < 30 min                                 | 20         |
| 30 min–1 h                               | 44         |
| Delayed hypersensitivity, i.e. latency   |            |
| 6–12 h                                   | 9          |
| > 12–24 h                                | 9          |
| > 1–2 days                               | 5          |
| > 2–3 days                               | 7          |
| > 3–6 days                               | 3          |
| > 6–12 days                              | 4          |

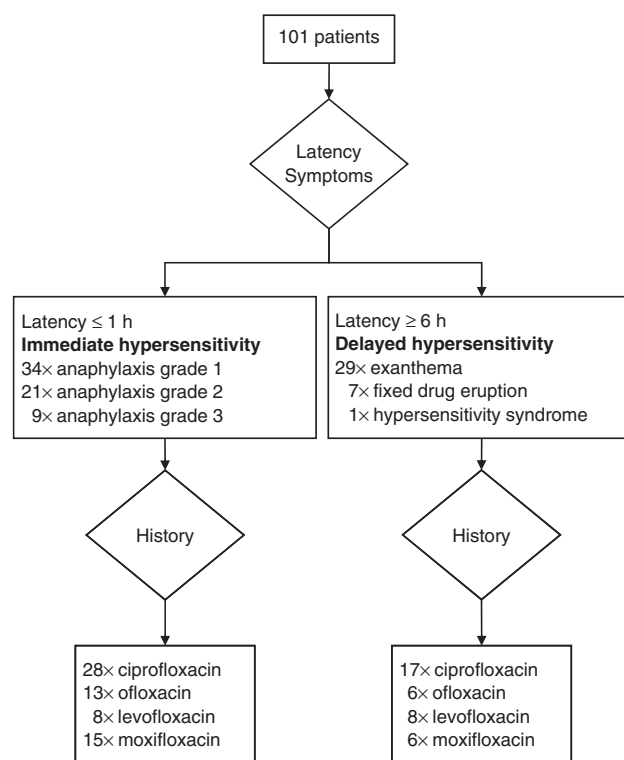


Fig. 1. Classification of the hypersensitivity reactions as immediate or delayed reactions and a list of suspected fluoroquinolones.

pathy, and elevated liver enzymes; severe generalized bullous skin reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis were not observed.

### Skin tests

The results of the diagnostic procedure are summarized in two separate flow charts: one for immediate and one for delayed reactions (Figs 2 and 3). Skin tests were applied corresponding to the clinical symptoms, i.e. immediate

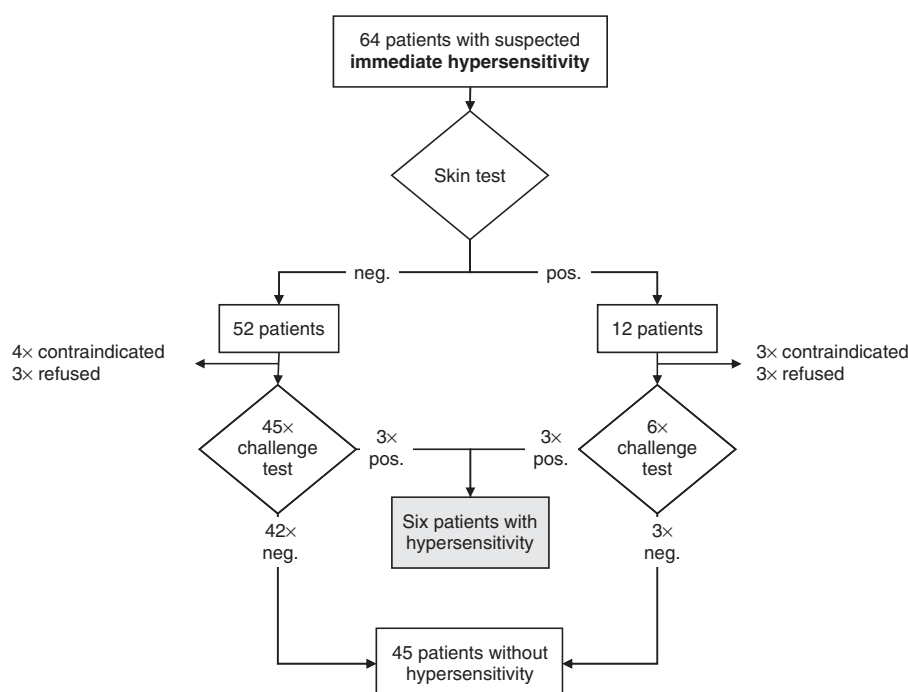


Fig. 2. Steps and results of the allergologic work-up in 64 patients with symptoms of an immediate reaction in temporal relation to fluoroquinolone treatment. neg., negative result; pos., positive result.

reading of prick tests after 20 min in patients with immediate reactions and delayed reading of prick and patch tests in delayed reactions, respectively. The time interval between the hypersensitivity reaction and the allergologic work-up was less than 1 year in all cases. In 12 patients, we observed positive immediate SPTs after 20 min (Fig. 2), whereas all skin tests in patients with suspected delayed hypersensitivity were negative (Fig. 3).

#### Tryptase measurement

Increased baseline serum tryptase levels (obtained either before the anaphylaxis event or at least 1 day after resolution of the clinical signs) as a symptom of systemic mastocytosis reflect an elevated mast cell burden and constitute a substantial risk factor for severe/hypotensive anaphylaxis [15, 20]. In 23 patients (including the nine reporting with grade 3 anaphylaxis), the tryptase serum level measured at least 3 weeks after the anaphylactic reaction was within the normal range.

#### Basophil activation test

In four patients with anaphylaxis symptoms after an oral challenge, no significant activation of basophils using different fluoroquinolones was seen (measured at least 3 weeks after the anaphylactic reaction) (Table 4). Positive controls with activating anti-FcεRI antibody yielded basophil activation between 40% and 60%.

#### Oral challenge

**Immediate hypersensitivity.** Fifty-one subjects out of 64 with a history of immediate hypersensitivity were orally challenged with fluoroquinolones (Fig. 2). Among them six patients responded with anaphylaxis symptoms. Interestingly, in all cases the symptoms only developed after the third or the fourth challenge dose (Table 4). All positive reactions were controlled by symptomatic therapy (antihistamines, glucocorticoids, inhalative β-mimetics) without adrenaline. Six patients refused challenge tests, and in seven patients, challenge tests were contra-indicated due to underlying severe cardiovascular disease or malignancy.

**Delayed hypersensitivity.** Two of 28 challenged patients (out of 37 with a history of delayed hypersensitivity) developed skin reactions: one had a maculopapular exanthema and the other suffered from a symmetrical intertriginous exanthema (Fig. 3, Table 4). In seven patients with a definite history and symptoms of a fixed drug eruption, in one patient with hypersensitivity syndrome, and in one patient with leukaemia, challenge tests were not performed.

In summary, fluoroquinolone hypersensitivity was excluded in 71 patients by performing the described allergologic work-up, i.e. skin tests and subsequent oral challenge tests.

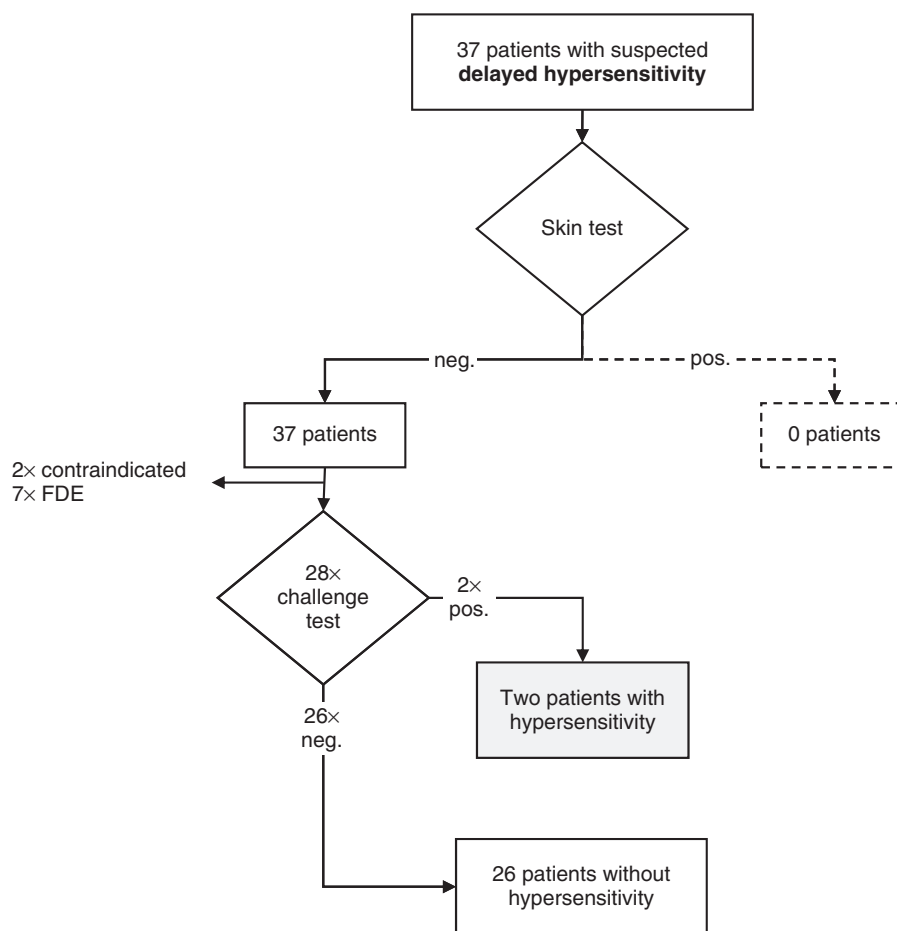


Fig. 3. Steps and results of the allergologic work-up in 37 patients with symptoms of a delayed reaction in temporal relation to fluoroquinolone treatment. FDE, fixed drug eruption; neg., negative result; pos., positive result.

Table 4. Results of skin and challenge tests in 8 patients with proven fluoroquinolone hypersensitivity

| Patient | Drug          | Skin test | BAT | Challenge test (latency) | Challenge test (symptoms) |                        |
|---------|---------------|-----------|-----|--------------------------|---------------------------|------------------------|
|         |               |           |     |                          | Anaphylaxis               | Delayed skin reactions |
| # 1     | Levofloxacin  | —         | —   | 50 min after third       | Grade 1                   | —                      |
| # 2     | Ofloxacin     | —         | ND  | 45 min after fourth      | Grade 1                   | —                      |
| # 3     | Moxifloxacin  | —         | —   | 1 h after fourth         | Grade 1                   | —                      |
| # 4     | Moxifloxacin  | +         | —   | 40 min after third       | Grade 1                   | —                      |
| # 5     | Ciprofloxacin | +         | —   | 30 min after fourth      | Grade 2                   | —                      |
| # 6     | Moxifloxacin  | +         | ND  | 1 h after third          | Grade 1                   | —                      |
| # 7     | Moxifloxacin  | —         | ND  | 20 h after fourth        | —                         | Exanthema              |
| # 8     | Ciprofloxacin | —         | ND  | 15 h after fourth        | —                         | SDRIFE                 |

Dose steps during challenge tests see Table 2. Grading system for anaphylaxis see Table 1.

ND, not done; —, negative result; +, positive immediate reaction of prick tests as described in "Material and Methods"; BAT, basophil activation test; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

## Discussion

The increasing use of fluoroquinolones in recent years might be one reason why fluoroquinolone hypersensitivity is nowadays more often suspected. Commonly, anaphylaxis

has been associated with fluoroquinolones, whereas delayed skin reactions have been reported rather infrequently. Importantly, in daily practice, and especially in drug reaction reports, the diagnosis of fluoroquinolone hypersensitivity is usually only based on history without further

diagnostic evaluation. However, our study shows that history alone is a vague and unreliable indicator of true fluoroquinolone hypersensitivity. Oral challenge tests rule out fluoroquinolone hypersensitivity in approximately 70% of the patients who had previously been labelled as such. Unfortunately, according to the literature [5, 6, 11, 21–23] and in our own experience, the results of fluoroquinolone skin or *in vitro* tests have to be carefully interpreted and often yield unreliable results. Therefore, oral challenge tests seem to be the only way to definitely diagnose or exclude fluoroquinolone hypersensitivity. However, oral challenge tests can only be performed in patients where the benefit of exclusion of a fluoroquinolone hypersensitivity outweighs the risk of the challenge test.

Prick and intradermal skin testing have been successfully applied in the assessment of IgE-mediated immunological drug reactions such as penicillin [14, 17]. Generally, prick tests are more specific but less sensitive than intradermal tests. In our study, fluoroquinolone prick tests proved not to be very helpful in determining hypersensitivity – however, the limited number of patients with definite immediate fluoroquinolone hypersensitivity does not allow the calculation of positive or negative predictive values. For intradermal testing, the concentrations administered have to be carefully adjusted because of the well-known irritant or histamine-releasing properties of fluoroquinolones. Several authors have identified optimal concentrations for intradermal testing ranging from 0.004 mg/mL for ciprofloxacin to 0.5 mg/mL for ofloxacin [22–24]. In our study, we abandoned intradermal testing because serial tests with, e.g., ciprofloxacin dilutions ranging from 0.0002 to 0.2 mg/mL yielded unreliable results, with positive reactions also in controls. Moreover, due to the considerable inter-individual variability of the test reactions, we were unable to identify a definite non-irritant concentration. Therefore, based on published data and our results, the significance of fluoroquinolone skin testing for patients with a history of immediate hypersensitivity symptoms remains a matter of debate.

Patch testing has been recognized as a reliable tool for diagnosing delayed hypersensitivity with the occurrence of delayed reactions at the skin test site, particularly for aminopenicillins [19]. Recently, in a study of T cell-mediated hypersensitivity to fluoroquinolones, positive patch test reactions to ciprofloxacin were observed in three out of five tested patients [9]. Otherwise, negative patch tests with fluoroquinolones in cases of confirmed delayed hypersensitivity have also been reported [25]. In cases with suspected fixed drug eruption, patch tests should be applied not only on the upper back but also in former lesional skin. In the literature, there is only one report of a positive lesional patch test in a fixed drug eruption due to ciprofloxacin, with negative results on normal skin [7]. In our 37 patients with a history of a delayed skin reaction, not a single patch test with fluoroquinolones was positive.

One cause for false-negative skin tests in patients with fluoroquinolone hypersensitivity may be that the culprit compound of the hypersensitivity reaction is not the parent drug itself, but a metabolite [26]. The methodical limitations of the described patch test procedure, e.g. vehicle and duration of occlusive exposure, may also explain the false-negative patch test results. Late readings of additional intradermal tests could increase test sensitivity in patients with suspected delayed hypersensitivity. However, intradermal testing at our allergy clinic is not routinely performed in cases with a history of a delayed reaction. The lymphocyte-transformation test (LTT) with fluoroquinolones as a further diagnostic method is not standardized yet, should only be performed in specialized laboratories, and interpretation of the results has to be very careful [9, 27].

Oral challenge tests are considered to be the gold standard to establish or exclude drug hypersensitivity [12]. Because the predictive value of fluoroquinolone skin tests appears to be low, careful controlled challenge testing with a progressive increase of doses may be attempted to verify or falsify skin test results. Before performing a drug challenge test, an assessment of the risk–benefit relationship has to be performed and careful surveillance of patients is mandatory. In our series, six patients with a suspected immediate hypersensitivity developed anaphylaxis symptoms within 5 h after the first of the total four doses of the stepwise oral challenge. Likewise, two patients with suspected delayed hypersensitivity developed late skin reactions between 15 and 20 h after the last dose. A negative result indicates that the patient is not sensitive at the time of the challenge test [28]. However, false-negative results can occur due to missing co-factors such as viral infection or exercise or due to tolerance induction by the challenge procedure [12, 29]. Theoretically, it is also possible that drug challenge tests lead to sensitization; however, this has not been shown to be relevant for, e.g., penicillins [30]. If a fluoroquinolone is required by a patient with a positive oral challenge, tolerance induction may be an option [31, 32].

In a previous study describing 55 patients with suspected fluoroquinolone-induced hypersensitivity, an IgE-mediated immune mechanism was shown in 30 patients by radioimmunoassay for determination of specific IgE in the serum [6]. However, challenge tests for confirmation of clinical relevance were not performed in this study. On the other hand, data from an animal model indicate that immediate hypersensitivity reactions may also be triggered by the direct non-specific histamine release from mast cells and basophils known from falsely positive skin tests [33, 34]. In this context, it has to be mentioned that all our six patients developed anaphylaxis during the challenge test not after the first or the second dose but only after the third or the fourth dose. This dose dependence and the prolonged latency are rather typical features of a non-allergic pathomechanism.

Commonly, fluoroquinolone-induced delayed skin reactions may present as maculopapular exanthema with or without resemblance to an infectious exanthema [5, 7, 35]. However, nine of our patients developed more specific skin eruptions. One patient with acute generalized exanthematous pustulosis has been classified as having hypersensitivity syndrome (DRESS) due to accompanying fever, lymphadenopathy, and elevated liver enzymes. Seven patients with repeated episodes of a clinically and histologically verified fixed drug eruption were not challenged. In one challenged patient, we observed an intertriginous exanthema, for which the acronym SDRIFE (symmetrical drug-related intertriginous and flexural exanthema) was recently proposed [36].

Our results of 71 patients with presumed fluoroquinolone hypersensitivity tolerating the suspected fluoroquinolone show that symptoms developing in temporal relationship with the intake of a fluoroquinolone may have been uncritically attributed to and misinterpreted as signs of hypersensitivity by patients and physicians. How can we explain the high frequency of incorrect diagnosis of fluoroquinolone hypersensitivity? Infectious diseases may lead to acute urticaria and angioedema. The most frequent reason for acute urticaria appears to be viral infections, especially of the upper respiratory tract, which are usually present a few days before the onset of weal formation [37]. The urticaria is then frequently attributed to the fluoroquinolone, which was taken concomitantly. Exanthema in temporal relationship with the application of a fluoroquinolone may have originated from causes other than the suspected drug, e.g. viral exanthema. Careful interpretation of anamnestic details before and after fluoroquinolone exposure is crucial. Also, other antimicrobial or non-steroidal anti-inflammatory drugs given concomitantly with the fluoroquinolone may trigger hypersensitivity symptoms.

In conclusion, non-allergic or allergic hypersensitivity may be one of the possible mechanisms of anaphylaxis symptoms or delayed skin reactions during fluoroquinolone therapy. In the majority of patients, skin or *in vitro* testing alone is not sufficient to identify fluoroquinolone hypersensitivity and on a risk-benefit assessment, oral challenge tests may be offered.

## Acknowledgements

There are no conflicts of interest and no funding.

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