

Negativity of the Basophil Activation Test in Quinolone Hypersensitivity: A Breakthrough for Provocation Test Decision-Making

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Key Words

Basophil activation test • Skin test • Provocation test •
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Abstract

Background: Quinolone hypersensitivity reactions are being more frequently reported. Skin tests in investigations of patients are known to not be fully reliable. The provocation test thus remains the gold standard in the definitive diagnosis of allergy, despite the risks involved. The aim of this study was to evaluate basophil activation tests (BATs) in the diagnosis of immediate-type reactions to quinolones. **Methods:** Thirty-four patients who presented an immediate-type hypersensitivity reaction less than an hour after quinolone administration were studied. The allergologic workup of these patients consisted of a careful clinical history, a skin test and a BAT with the culprit quinolone. If not contraindicated, and in the case of high probability of a nonallergic reaction, provocation tests were performed to assess the nonimmunologic nature of the hypersensitivity. **Results:** Among the 34 patients studied, 17 (50%) presented a negative BAT to the suspected quinolone, while the other 17 (50%) patients presented a positive BAT for quinolone at the time of their reaction. Among the 17 patients with negative BATs, 15 (2 of whom had had positive skin tests) had quinolone success-

fully reintroduced. **Conclusions:** Our report suggests that the BAT, if negative for the culprit quinolone, is a valuable tool in the decision whether or not to perform provocation tests in patients with a history of immediate-type reaction to quinolones, in order to exclude an allergic reaction.

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Introduction

Quinolones are synthetic antibiotics largely used due to their broad range of activity against both Gram-positive and Gram-negative bacteria and their good safety profile. However, some adverse effects have been reported including immediate-type hypersensitivity reactions. These reactions, ranging from urticaria to shock, often occur within 1 h after the intake of quinolones; they can be classified either as immune allergic reactions (IgE mediated) or as nonallergic reactions [1, 2]. The distinction between these two mechanisms is of particular interest in order to exclude this family of antibiotics to prevent future accidents in the case of a true allergy. To date, the diagnosis is still mainly based upon

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a significant clinical history and skin tests, due to the lack of validated laboratory tests. Unfortunately, skin tests are known to display poor characteristics in the diagnosis: both false negative [3] and false positive [4] results have been described. Thus, the provocation test, although not without risk, remains the gold standard in the definitive diagnosis. In 2004, Manfredi et al. [2] documented the presence of specific IgE against quinolones for the first time, using an original radioimmunoassay. More recently, using a similar technique for IgE detection, Aranda et al. [5] have compared specific IgE and basophil activation test (BAT) sensitivities in the diagnosis of quinolone hypersensitivity. In our study we want to highlight the excellent negative predictive value of BAT in the diagnosis of immediate-type reactions to quinolones; this is very helpful in the decision to perform the provocation test.

Patients and Methods

Patients

Thirty-four patients who presented an immediate-type hypersensitivity reaction less than an hour after quinolone administration were studied. The demography and the clinical data of these patients are presented in table 1. The allergologic workup of these patients consisted of a careful clinical history, a skin test and a BAT with the culprit quinolone; this was performed within the first 4 months following the adverse reaction. If not contraindicated, and in the case of high probability of a nonallergic reaction, provocation tests were performed to assess the nonimmunologic nature of the hypersensitivity.

BATs

BATs against culprit drugs were performed measuring CD203c [6] expression in the basophil population. The positivity threshold was defined using a negative control without any drug. Anti-IgE was used as a positive control. All the results were expressed as a percentage of CD203c-positive basophils among the total basophil population. Three drug dilutions were tested (1, 0.5 and 0.1 mg/ml). Results were considered positive when at least two sequential drug dilutions induced more than 10% CD203c-positive basophils above the negative control value [6].

Skin Tests

Prick tests were the first step (with drug concentrations ranging from 2 to 40 mg/ml, depending on the drug, see table 1) and if these were negative, intradermal tests at low concentrations (1/1,000, 1/100 dilutions of the prick solutions) were performed.

Provocation Tests

When a provocation test was performed, a single-blind placebo-controlled oral provocation was carried out using the culprit quinolone. It was conducted in an intensive care unit if the initial reaction had been severe (grade 2 or 3) or under strict medical monitoring in the other cases.

Table 1. Clinical data of the 34 patients

Mean age (range), years	48 (17–85)
Sex ratio, M/F	8/26
Severity of the reaction	
Grade 1	11 (32%)
Grade 2	7 (21%)
Grade 3	16 (47%)
Culprit quinolones (prick test concentration)	
Levofloxacin, 5 mg/ml	11
Ofloxacin, 5 mg/ml	8
Ciprofloxacin, 2 mg/ml	4
Moxifloxacin, 40 mg/ml	4
Lomefloxacin, 40 mg/ml	3
Flumequin, 40 mg/ml	2
Norfloxacin, 40 mg/ml	1
Pipemidic acid, 40 mg/ml	1

Results

Among the 34 patients studied, 17 (50%) presented a negative BAT to the suspected quinolone (fig. 1). The skin tests of these 17 patients were negative for 13, and positive for 4. All 13 patients who presented both negative skin tests and negative BAT were reintroduced successfully, herewith confirming the nonallergic origin of their initial reaction. Among the other 4 patients, with positive skin tests and negative BATs, 2 were also defined as nonallergic since they underwent a successful provocation test with the culprit drug. The provocation tests were not performed in the last 2 patients due to ethical considerations concerning the severity of their initial reaction.

The other 17 patients presented a positive BAT for the culprit quinolone (fig. 1). Among these 17 patients, 13 also presented positive skin tests. In these 13 patients, the combination of highly significant clinical histories (i.e. severe symptoms, rapid onset), positive skin tests and positive BATs strongly suggested allergic reactions, and provocation tests were therefore not performed. In 1 of the 4 other patients presenting negative skin tests, a provocation test was performed; this test was positive, enabling us to conclude the allergic nature of the reaction. Provocation tests were not performed in the 3 other patients due to ethical considerations, and thus one cannot definitively conclude the allergic nature of their reaction.

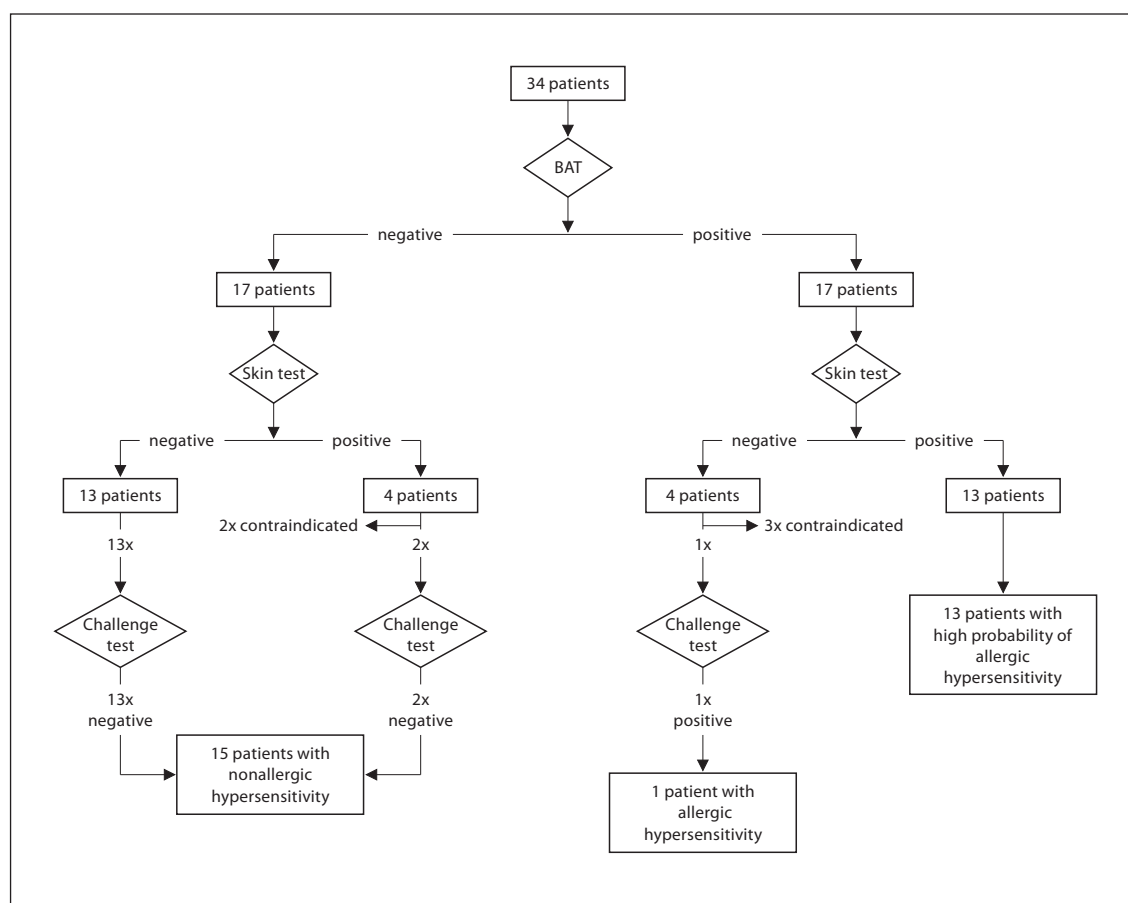


Fig. 1. Steps and results of the allergologic workup in 34 patients with a highly significant history of immediate allergic reaction to quinolones.

Discussion

Our results are consistent with the data reported by Manfredi et al. [2], who found a positivity of 54.5% for specific IgE in a population of patients with an immediate-type hypersensitivity reaction. In contrast, in a similar population, Aranda et al. [5] reported a discrepant sensitivity between specific IgE (positivity of 31.6%) and BAT (positivity of 71.1%). Nevertheless, BAT sensitivity to quinolone is yet to be established, as Seitz et al. [7] described no positive results in a small sample of 4 allergic patients.

Our study thus confirms that skin tests are not really reliable in the investigation of a hypersensitivity reaction to quinolones, since 1 false negative and 2 false positive skin tests were documented in our cohort of 34 patients. False positivity of intradermal tests can be explained by the nonspecific histamine-release potency of quinolones

[8]. Today, it is generally agreed that the provocation test is considered the sole definitive diagnosis in quinolone allergy [1, 2, 9]. Though these tests are of crucial interest in order to not exclude the quinolone family on the simple basis of a suggestive clinical history or skin tests (which can be falsely positive), they might nevertheless be dangerous [10] and the risk-benefit ratio must be carefully considered. In this context, our study clearly highlights the excellent negative predictive value of BAT in the care of patients with a significant clinical history of immediate-type reactions to quinolones; all 15 patients presenting negative BATs (2 of whom had had positive skin tests) and on whom a provocation test was performed, had the culprit drugs successfully readministered. In conclusion, BAT is a valuable tool in the decision to perform provocation tests in patients with a history of immediate-type reactions to quinolones.

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