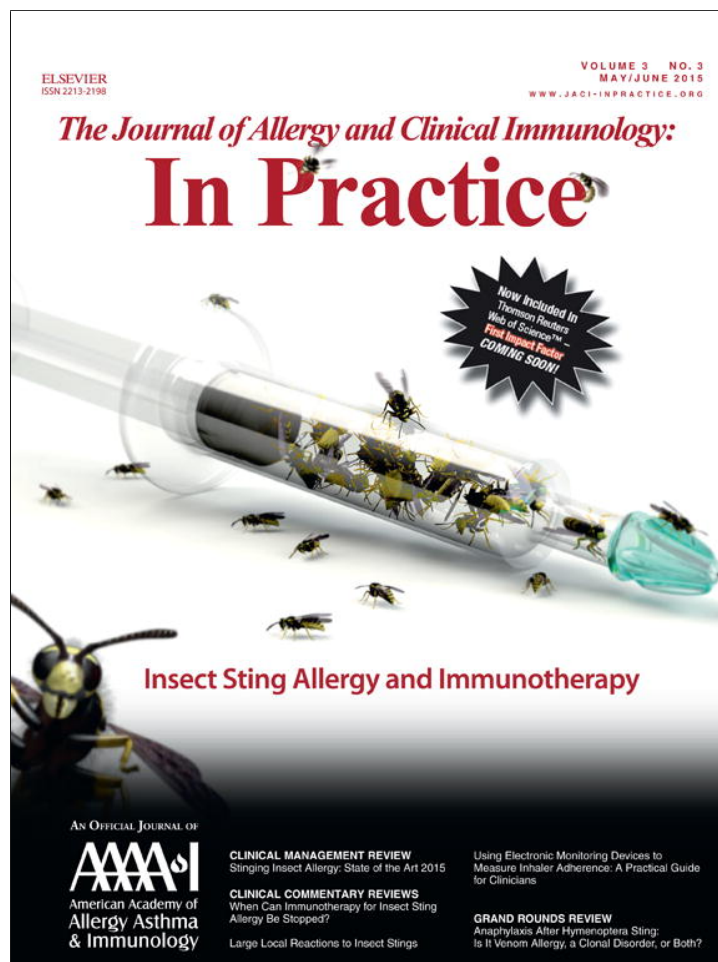




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Clinical Communications

Moxifloxacin hypersensitivity: Uselessness of skin testing

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Clinical Implications

- Skin prick and intradermal testing with moxifloxacin are unreliable methods to establish a diagnosis of moxifloxacin hypersensitivity. Higher dilution skin tests remain negative in the majority of patients with prior reactions, whereas higher concentrations are not discriminative between patients and exposed control individuals.

TO THE EDITOR:

Quinolones are synthetic antibiotics based on the 4-quinolone and 1,8-naphthyridine nuclei. They can cause severe hypersensitivity reactions, even after first exposure, with moxifloxacin being an important culprit.¹ Unfortunately, a diagnosis of quinolone hypersensitivity is not straightforward, because of the absence of drug-specific sIgE immunoassays and uncertainties associated with skin testing with potentially nonspecific histamine releasers.^{2,3} These contradictory studies show that establishing nonirritating skin-test concentrations for ciprofloxacin is not straightforward. For example, Broz et al³ recommend an intradermal test (IDT) concentration of 1:300 to 1:1000 in saline for ciprofloxacin. In contrast, the Empedrad study² failed to determine a nonirritating concentration for ciprofloxacin because the irritating concentration varied a 1000-fold in healthy volunteers. Accordingly, the European Network on Drug Allergy and European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group has made no drug-specific recommendations about skin prick test (SPT) and/or IDT with quinolones.⁴ For moxifloxacin, the literature reveals “nonirritant” concentrations for SPT to vary between 1 and 20 mg/mL and for IDT between 0.004 and 0.05 mg/mL.⁵⁻⁹ However, inspection of the data discloses that 3/5 studies did not include controls⁶⁻⁸ and data gathered in patients were restricted to a maximum of 5 cases.^{5,7-9}

This study assessed SPT and IDT in the diagnosis of immediate moxifloxacin hypersensitivity. A comparative study was performed between patients with histories of reactions and controls who tolerated a graded oral drug provocation test (DPT) with moxifloxacin. Patient inclusion was based on clinical history. Fourteen patients with a history of an immediate hypersensitivity reaction to moxifloxacin were enrolled. All patients suffered from urticaria/angioedema, bronchospasm/hypotension, and/or loss of consciousness within 60 minutes after intake. Other possible causes were excluded (ie, concomitant intake of other drugs). Time between reaction and investigation ranged between 0.3 and 21 months (median: 4 months) (Table I). Sixteen individuals who tolerated a graded oral DPT served as an exposed-control group.

Skin testing consisted of SPTs and IDTs with a parenteral formulation of moxifloxacin hydrochloride (Avelox 400 mg/250 mL

[or 1.6 mg/mL], Bayer SA-NV, Diegem, Belgium). SPT was performed using a 1:10 dilution and undiluted moxifloxacin. Results were considered positive when wheal/flare equaled or exceeded 3/3 mm. For IDTs, serial dilutions of 1:1000, 1:100, and 1:10 were used. Results were considered positive when the wheal equaled or exceeded 5 mm.

Patients with a history of betalactam hypersensitivity are more prone to develop hypersensitivity reactions to fluoroquinolones.¹⁰ Because the majority of subjects included as controls consulted with such a history, we preferred a graded DPT instead of a full dose provocation in search of a safe alternative. All controls had a negative oral graded DPT with moxifloxacin (Avelox) up to a cumulative dose of 750 mg.

Statistical analysis was performed with IBM SPSS Statistics 22 (IBM Corp, Armonk, New York). Fisher's exact tests were used to evaluate significance differences of the skin-test results between patients and controls.

SPT and IDT results are displayed in Figure 1. SPT was negative in all patients and controls. Intradermal testing yielded positivity in 10/14 patients. Two patients tested positive at the 1:1000 dilution (0.0016 mg/mL), 2 patients at the 1:100 dilution (0.016 mg/mL), and 6 patients at the 1:10 dilution (0.16 mg/mL). Of the 14 patients, 4 displayed a negative SPT and IDT.

In controls, IDT was also positive in 12 individuals. Of the 16 individuals, 2 tested positive at the 1:100 dilution. Of the 14 individuals who received the 1:10 dilution, 12 tested positive. The remaining 2 manifested a (true) negative result in both SPT and IDT.

Sensitivity and specificity of the intradermal testing calculated between patients and controls in this population were 57% and 12.5%, respectively. Positive and negative predictive values were 36% and 25%, respectively. A comparison of IDT between patients and controls yielded *P*-values of .192 for the 1:1000 dilution, 1.00 for the 1:100 dilution, and .209 for the 1:10 dilution.

This is the first assessment of skin testing for moxifloxacin with a comparative study between patients and controls who tolerated a cumulative dose of 750 mg moxifloxacin during a graded oral DPT. We conclude that SPTs and IDTs with moxifloxacin hydrochloride are unreliable methods to establish a diagnosis of immediate moxifloxacin hypersensitivity. Our data are in line with previous findings that quinolones frequently induce skin-test responses in healthy subjects.^{2,3} It appears that at higher dilutions skin tests remain negative in a majority of patients, whereas higher concentrations are not discriminative between patients and exposed controls.

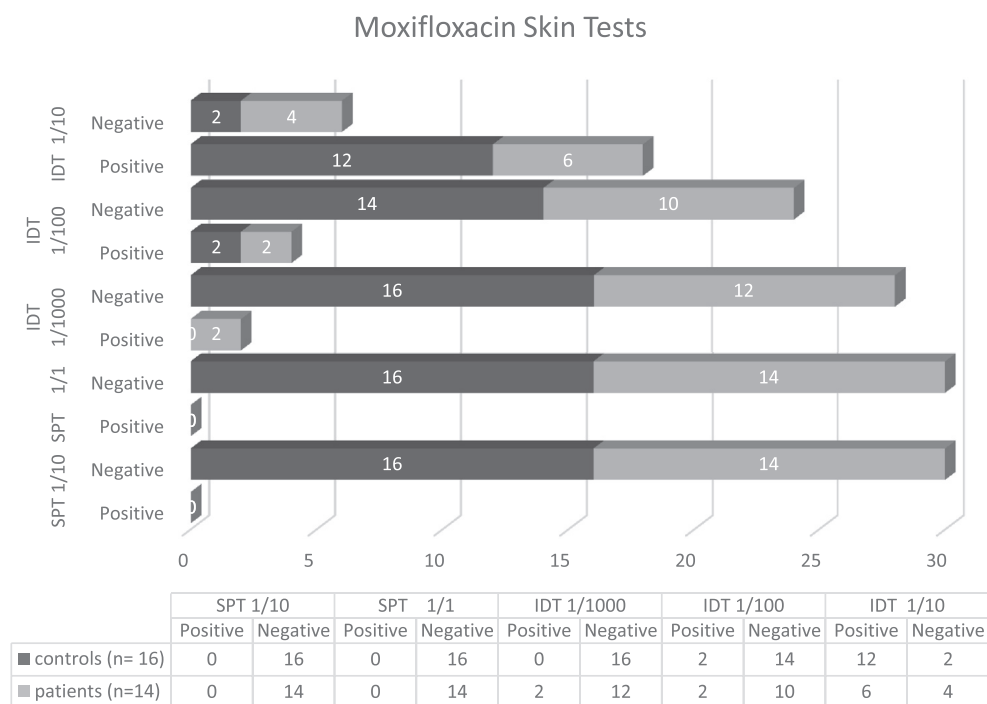
There are studies that show that the time elapsed between the acute reaction and skin tests affects the outcome of the tests, which makes it difficult to interpret.¹⁰ We were unable to assess such an effect because the majority of patients received skin testing within 6 months after the acute reaction, and a longitudinal follow-up study does not seem to be warranted.

A limitation of our study is the absence of controlled DPTs as previous research has shown that as few as 1/3 of patients with similar recent convincing reaction histories to quinolones reacted on being challenged with the culprit drug.¹⁰ However, because the time between the reactions and evaluation was relatively short

TABLE I. Demographics, clinical manifestations, and skin-test results in the patients with histories of reactions to moxifloxacin

Patient	Sex	Age (y)	Clinical symptoms within 1 h after intake of moxifloxacin	Skin test	Time between reaction and skin testing (mo)
1	F	39	Urticaria, angioedema, dyspnea, and loss of consciousness	Positive IDT 1/100	Unknown
2	F	62	Urticaria, dyspnea, tachycardia, hypotension, and desaturation	Positive IDT 1/10	21
3	F	36	Urticaria, angioedema, dyspnea, and vomiting	Negative	4
4	F	63	Urticaria, angioedema, dyspnea, and hypotension	Positive IDT 1/10	0.3
5	F	36	Angioedema, hypotension, and vomiting	Positive IDT 1/10	3
6	M	55	Urticaria, angioedema, dyspnea, and palpitations	Negative	4
7	F	41	Urticaria, angioedema, hypotension, dyspnea, and nausea	Positive IDT 1/1000	4
8	M	32	Urticaria, angioedema, and dyspnea	Positive IDT 1/10	18
9	F	47	Urticaria, angioedema, nausea, dyspnea, and vertigo	Positive IDT 1/1000	2
10	F	60	Urticaria and dyspnea	Negative	5
11	F	25	Angioedema and dyspnea	Positive IDT 1/10	4
12	F	54	Urticaria and dyspnea	Positive IDT 1/100	4
13	F	63	Urticaria, angioedema, hypotension, and stridor	Positive IDT 1/10	5
14	F	49	Angioedema, abdominal cramps, and loss of consciousness	Negative	Unknown

F, female; IDT, intradermal test; M, male.

**FIGURE 1.** Skin test results in patients and control individuals. *SPT*, skin prick test; *IDT*, intradermal test.

in most patients (Table I), we deemed DPT unethical and unnecessary.

To date, DPT remains the gold standard to establish the diagnosis of drug allergy. However, for obvious safety and

practical reason, this is not always feasible. Given the lack of sensitivity and specificity of skin tests, the unavailability of well-validated quinolone-specific sIgE assays, and the controversy about the specificity of some home-made methods,¹¹ there is

need for other reliable methods to establish the diagnosis of moxifloxacin hypersensitivity.

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