

Usefulness of basophil activation tests for the diagnosis of IgE-mediated allergy to quinolones

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IgE-mediated allergy to quinolones (Q) is rare and its diagnosis is hampered by the lack of sensitive *in vivo* or *in vitro*

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assays (1). Skin tests have an as yet unknown sensitivity because of the high incidence of false-positive results, probably related to direct quinolone-induced histamine release by mast cells (2). Recently, Manfredi et al. (3) reported on an *in vitro* assay able to detect specific IgE in quinolone allergic patients using a radio-immuno-assay and IgE binding inhibition test. However, this assay is not available for routine *in vitro* diagnosis of Q allergy. In the present study, we report on the use of the basophil activation test for the diagnosis of Q allergy.

Five patients with a clinical history of immediate hypersensitivity (IHS) to Q are described in Table 1. They all developed an anaphylactic reaction 5–45 min following the first taking of one tablet of levofloxacin, ofloxacin or moxifloxacin. The symptoms improved rapidly following adrenaline, antihistamines or corticosteroids injection.

Skin tests and immunological tests were performed 1–4 months after the reaction. Two series of skin tests were performed. The first series tested the Q involved in the hypersensitivity reaction using prick tests (5 mg/ml) and intradermal tests (IDT) (5 µg/ml). Skin tests were positive in the five patients, confirming the diagnosis of immediate allergic HS (Table 1). Controls included prick and IDT to the solvent, which were negative in the five patients. Skin tests to Q were negative in control patients who had never experienced a Q-induced HS reaction. The second series of skin tests (prick and IDT) was performed in patients 1 and 4 only, to test for potential cross-reactivities of patients' specific IgEs to other members of the quinolone family (ofloxacin, levofloxacin, norfloxacin, moxifloxacin, peflacin, pipemidic acid and moxifloxacin). Skin tests were negative for all additional Q tested in patient 4

Table 1. Patients Characteristics, skin test, basophil activation test (BAT) and re-administration

Patient	Age Sex	Culprit drug	Type of reaction	Delay before reaction (min)	Skin tests		BAT CD203c		Quinolone Re-administration
					Culprit Q	Other Q(1)	Culprit Q	Other Q(1)	
1	18 Female	Ofloxacin	Hypotension, dyspnea, oral pruritus urticaria	45	Positive Prick	Positive Prick (Levofloxacin)	Positive 70% (control 2%)	Positive Levofloxacin (BAT 46%)	Norfloxacin (1 tab. 400 mg) Ciprofloxacin (1 tab. 400 mg)
2	65 Female	Levofloxacin	Malaise, thoracic pain, dyspnea, angioedema	45	Positive Prick	Negative	Positive 71% (control 2%)	ND	ND
3	71 Female	Levofloxacin	Malaise, hypotension, urticaria, angioedema, coma	30	Positive IDT	Negative	Positive 71% (control 2%)	ND	ND
4	61 Female	Ofloxacin	Malaise, hypotension, urticaria, angioedema, coma	5	Positive Prick	Negative	Positive 83% (control 1%)	Negative	Norfloxacin (1 tab. 400 mg) Peflacin (1 tab. 250 mg)
5	77 Female	Moxifloxacin	Anaphylactic shock	Immediate	Positive Prick	ND	Positive 80% (control 1%)	ND	ND

ND, not done; IDT, intradermal test; Q, quinolones.

who, therefore, was sensitized to ofloxacin only. In contrast, patient 1 developed positive prick tests to levofloxacin and was considered sensitized to both ofloxacin and levofloxacin.

The basophil activation test (BAT) analyzing by FACS the expression of CD203c on the patient's basophils was carried out on patient's serum. The results are expressed as % of basophils expressing CD203c after *in vitro* re-stimulation with Q compared to this % without *in vitro* re-stimulation (controls in Table 1). Additional experiments demonstrated that basophils from healthy individuals did not upregulate CD203c after stimulation by Q. Basophil activation test to the culprit Q was strongly positive in the five patients. Indeed, 70–83% of basophils expressed CD203c upon Q exposure compared to a control expression ranging from 1% to 2%. Next, the BAT was used to test for potential cross-reactivities in patients 1 and 4. In patient 4, sensitized to ofloxacin, the BAT was negative for all additional Q tested. In contrast, in patient 1, sensitized to ofloxacin, the BAT was positive for levofloxacin (46% *vs* control 2%). As patients 1 and 4 needed Q, these two patients were given ciprofloxacin (400 mg), norfloxacin (400 mg) and pefloxacin (250 mg) orally. Both Q were well tolerated and did not induce any HS reaction.

IgE-mediated allergy to Q is rare. The skin tests (prick and IDT) are thought to

be of poor diagnostic value (1, 4), although our data do not confirm this hypothesis. Indeed, we show here that skin tests are positive in five of five patients with a typical history of allergic IHS to Q. Interestingly, the CD203c BAT was able to diagnose the five patients as IgE-mediated allergic to Q. The BAT (basophil activation test) using flow cytometry has been developed as an alternative method for *in vitro* diagnosis of IgE-mediated reactions to various allergens, including drugs (5). Basophil activation is associated with upregulation of CD203c expression and neo-expression of CD63. Although CD63 and CD203c BAT measure basophil activation to a similar extent, recent studies have shown that CD203c is more sensitive than CD63 for the diagnosis of IgE-mediated allergy to beta-lactams(6).

In conclusion, the CD203c BAT appears to be a useful assay for the diagnosis of Q allergy, allowing for the study of cross-reactivities among Q antibiotics and permitting a better management of Q allergic patients.

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